ANALYSIS OF PROGRAM ACTIVITIES
NATIONAL INSTITUTES OF HEALTH
1955

NATIONAL INSTITUTE OF
NEUROLOGICAL DISEASES AND BLINDNESS

NATIONAL INSTITUTES OF HEALTH
PUBLIC HEALTH SERVICE
U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

United States. National Institute of Neurological
Diseases and Blindness.
Report of program activities.

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases & Blindness
INSTITUTE

2. Office of Director
LABORATORY OR BRANCH

3. ______
SECTION

4. ______
LOCATION (IF OTHER THAN BETHESDA

5. NINDB-OD-1
SERIAL NO.

6. Administration
PROJECT TITLE

7. Pearce Bailey, M.D., Director, Dr. Henry Imus, Assistant to the Director and Eckart Wipf, Administrative Officer
PRINCIPAL INVESTIGATORS

8. 5 Secretaries
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

This project finances the office of the Institute Director and his immediate staff for the overall program direction and administration for the National Institute of Neurological Diseases and Blindness.

12. ______
BUDGET ACTIVITY: ADMINISTRATION

13. ______
IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

None

14. ______
IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

Not applicable

RC
346
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1955
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R.P.C. - 1
January 1956

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Cerebral Palsy Project
LABORATORY OR BRANCH

3. Medical Neurology
SECTION

4. ______
LOCATION

5. NINDB-OD-2
SERIAL NO.

6. Collaborative Study of Cerebral Palsy
PROJECT TITLE

7. Pearce Bailey, M. D.
PROGRAM DIRECTOR

Henry A. Imus, Ph. D.
PROJECT DIRECTOR

8. G. Milton Shy, M. D., Maitland Baldwin, M. D., Anatole S. Dekaban, M. D., William F. Windle, Ph. D., J. Gordon Millichap, M. D. (Dr. George W. Anderson, Johns Hopkins Hospital, Consultant)
INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To discover and/or evaluate genetic and environmental factors of etiological significance in cerebral palsy. By means of collaborative field investigations, as well as intramural studies, to correlate the clinical findings of cerebral palsied patients with subsequent pathological findings obtained at autopsy.

Methods Employed: This study will be conducted in two ways. (1) Collaborating institutions will select infants showing signs of stress at birth, or showing neurological symptoms in the postnatal period. The detailed prenatal, natal, and postnatal data on these cases will be collected, and the individuals will be studied clinically. Normal babies will be used as controls. Less detailed information will be obtained on the immediate family of each subject used in the study. In the event of death, an autopsy will be performed and the intact brain and spinal cord, or representative microscopic sections, will be sent to the NINDB together with the complete records on the case for further study and analysis. These findings will be collated with data on cases submitted by other collaborating institutions. Complete records will be made by the NINDB to each collaborator. (2) In certain collaborating institutions having custodial care of cerebral palsied patients, intensive clinical studies will be made, and efforts will be made to collect perinatal histories. When these cases come to autopsy, the intact brain and spinal cord, or representative microscopic sections, will be sent to the NINDB for further study and for clinicopathologic correlations.

Each participant will be completely free to do as much of the analyses of their own material as they desire and to publish their reports independently. The analyses prepared by this Institute will be submitted to the participants, and a statistical report of the results of all of the work will be published and distributed by the central laboratory.

Patient Material: Patients will be studied at the Clinical Center of the National Institutes of Health and at collaborating institutions in various parts of the United States. The cerebral palsy patients will be admitted to the study as soon as possible after the diagnosis has been made.

Major Findings: With many and variously trained personnel collecting information and pathological material, it is essential that a carefully prepared protocol be developed for the collection of patients' histories and pathological specimens. To accomplish this, fifteen scientists, under the Chairmanship of Dr. H. Houston Merritt, met on March 18-19, 1955, at the National Institute of Neurological Diseases and Blindness. These scientists represented various fields of medicine, including embryology, neurology, pathology, neuropathology, psychology, obstetrics, pediatrics, and orthopedics.

The protocol, which they developed, includes requirements for information on family history, mother's history, the record of events at birth, clinical history, the record of clinical examinations, and a complete record of pathological examinations, including specific details for the removal, sectioning, and preservation of the brain and spinal cord. This protocol is now being subjected to practical test. Concurrently, institutions which might collaborate in the study are being invited to submit proposals for consideration by the National Advisory Neurological Diseases and Blindness Council.

Significance to the Cerebral Palsy Research Program: It is anticipated that the increased understanding of the etiology and the clinicopathologic correlations gained by this study will lead to better terminology, classification, prophylaxis, and treatment in the field of cerebral palsy. Furthermore, this investigation should provide valuable leads for future research in this field.

Proposed Course of Project: After the protocol has been given further preliminary trial, and the collaborating institutions have joined the project, the collection of data and autopsy material will begin.

10. NINDB-OD-2
SERIAL NO.

11.

12.

13. None

14. NINDB-L-9. A study with primates on the experimental production of anomalies similar to cerebral palsy by means of asphyxia at birth, drugs commonly used in obstetrical practice and other methods. Wherever possible, the results of this study will be related to corresponding material from humans in the collaborative project.

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description

1. National Institute of Neurological Diseases and Blindness
INSTITUTE

2. None
BRANCH

3. Publications and Reports
SECTION

4. Bldg.8~~9~~ - NIH
LOCATION

5. NINDB OD-3
SERIAL NO.

6. Scientific Information and Education Activities
PROJECT TITLE

7. Frank O. Barden, Jr., Chief Dorothy Horlander
PRINCIPAL INVESTIGATOR (S)

8. Two Secretaries
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

It is the responsibility of this section to supervise, plan, and coordinate the collection, editing, assembly, review, clearance, presentation or dissemination of information pertaining to neurological and sensory diseases and disorders to federal departments and agencies; to voluntary and private organizations; and, to the general public; to provide assistance to scientist in professional communications which are their responsibility; to plan and direct an integrated program of information and education designed to improve the state of public opinion regarding the research being conducted, the treatment and prevention of such disorders as cerebral palsy, epilepsy, multiple sclerosis, muscular dystrophy, cerebral vascular disease, glaucoma, cataract, uveitis, deafness, and mental retardation.

The section is primarily concerned with activities which include:

1. Formulation of policy for editing, revising, or rewriting manuscripts, bulletins, releases, pamphlets, visual presentations, and other materials for publication or dissemination; searching for, writing, or

revising material, verifying references and tables, preparing title pages, tables of contents, and indexes, and proofreading; planning or execution of informational, public relations, educational, or interpretative campaigns and materials, contacting sources of information and arranging for the preparation and dissemination of information by such means as publications, press, radio-TV, visual presentations, or other media in order to inform the public about or cultivate interest in the activities and programs of the Institute.

2. Acquainting scientific and professional groups and the public with the work of the Institute by means of planning and utilization of exhibits, illustrated lectures or film strips, public displays, charts, and other visual media, and determining the public's need for or lack of information about the Institute's programs and objectives and the analysis of public attitudes or reactions toward these objectives and information programs.

3. Preparation of weekly, quarterly, and annual reports on program activities to NIH, PHS, and DHEW, including research highlights and progress reports; drafting of statements and testimony for the congressional Appropriation Committees for the Director.

4. Handling of public inquiries approximately 4,500 per year on disease entities, research findings, methods and sources of treatment and rehabilitation, and requests for admission to the Clinical Center for participation in the Institute's research studies.

5. Preparation of agenda and materials, speeches, lectures, meetings, and symposiums for presentation by the Director of the Institute and members of the staff to scientific and lay organizations, and counsel and advice on information to assure acceptance of those materials, coordination of special projects with voluntary health organizations and assistance to science writers

and members of the press interested in articles on neurological and sensory disorders, development of uniform procedures, standards, methods, and techniques for the presentation of information to implement translation of NIH policies and NINDB programs with scientific, professional, private and public groups interested in the present knowledge and developments in the field of neurological and sensory disorders.

The chief of the section serves as the Institute representative at Scientific Reports Branch-NIH internal staff and policy determining meetings; represents the Director at press conferences and meetings with representatives of those government or private groups concerned with the functions, missions, objectives, and projects of the Institute; performs other duties as assigned by the Director.

During FY 1956, the increase in the work load of this section has resulted in the addition of space and in recruiting activities for a professional science writer. Activities include initial planning in preparation of pamphlets on "The Institute of Neurological Diseases and Blindness", "Cerebral Palsy", "Epilepsy", "Muscular Dystrophy", and "Research in the Blinding Diseases"; initial planning for motion pictures on cerebral palsy and epilepsy; planning and programming of exhibits on the Institute's collaborative projects, and the revision of present exhibits for presentation at future scientific meetings.

10. & 11.--- not applicable.

12. Research
BUDGET ACTIVITY

13. & 14. --- not applicable.

15. Not applicable.

16. None.

17. None.

R. P. C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Neurological Diseases and Blindness
INSTITUTE

2. Extramural Programs
LABORATORY OR BRANCH

3. [illegible]
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NINDB-EP-1
SERIAL NO.

6. Research Grant Program
PROJECT TITLE

7. Alfred Weissler, Ph. D. and Gordon Seger, Dr. P. H.
PRINCIPAL INVESTIGATORS

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective: To advance the prevention, diagnosis, and therapy of neurological and sensory diseases, by support of basic and applied research in these fields at non-governmental institutions.

Method employed: Grants are made on the basis of scientific review of applications requesting funds to provide salaries, equipment, supplies or other items needed in the pursuit of medical research. Applications contain a detailed description of the research planned and other data necessary to scientific evaluation.

Major fields of emphasis: During the calendar year 1955, 422 research grants totalling $4,463,101 were awarded in this program. These have supported research projects conducted in 64 medical schools and 55 other non-federal research institutions throughout the country. In addition, 38 applications requesting a total of $473,276, which were recommended for approval by reviewing panels, could not be

Analysis of NIH Program Activities

Project Description Sheet

paid for lack of funds; also, 63 requests for an aggregate of $820,104 were received which review committees failed to recommend for support.

The projects supported involve research into the causes, care, and treatment of diseases and conditions of the brain, spinal cord and peripheral nerves, sensory endings, eye, and ear. Such specific disorders as cerebral palsy, muscular dystrophy, epilepsy, multiple sclerosis, cerebral vascular accidents, mental retardation, glaucoma, cataracts, retrolental fibroplasia and other blinding eye conditions, and impairments of hearing, balance, and speech are included in projects presently active.

Significance to Neurological and Sensory Disease research: Continued progress in the effort to prevent and control neurological and sensory disorders depends on the improved quality and quantity of related research made possible by this grant program. In some instances, as in retrolental fibroplasia, fundamental biological investigations disclose a path to a major advance in preventive medicine; in other cases, a concerted collaborative effort by many institutions results in a saving of several years in the development of an improved therapeutic procedure.

Proposed course of project: To continue supporting those presently active projects which may be recommended by our scientific and advisory review groups. To support new projects insofar as funds allow in order that the efforts of more medical and research manpower may be brought to bear on problems in the neurological and sensory disease fields involving such disciplines as neuroanatomy, neurophysiology, neuropathology, neurobiochemistry, neurology, ophthalmology, otolaryngology, etc.

R. P. C. -3
December 1955

Analysis of NIH Program Activities

Project Description Sheet

10. NINDB-EP-1
SERIAL NO.

12. BUDGET ACTIVITY: Review & Approval

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 OR 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

None providing funds, facilities, or personnel.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE, IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

This program complements the research grant program of other Institutes at NIH.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

None orginating from this office. Grantees, however, publish freely.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

None.

R. P. C. -1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Neurological Diseases and Blindness
INSTITUTE

2. Extramural Programs
LABORATORY OR BRANCH

3. ______
SECTION

4. ______
LOCATION (IF OTHER THAN BETHESDA)

5. NINDB-EP-2
SERIAL NO.

6. Research Fellowship Program
PROJECT TITLE

7. Gordon H. Seger, Dr. P. H.
PRINCIPAL INVESTIGATORS

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objective: To create and maintain a resevoir of highly trained personnel competent to carry out laboratory research in the fields of neurological and sensory disorders.

Method employed: On the basis of a careful review of applications and supporting information, awards are made to a small number of the most promising candidates to enable them to obtain research training and experience. These awards averaging $3600 each are made at the predoctoral, postdoctoral and senior scientist level.

Major fields of emphasis: During the calendar year 1955, 40 fellowships were awarded consisting of 13 at the predoctoral level in the amount of $31,866, 24 postdoctoral awards amounting to $99,715; and 3 special fellowships involving $12,717. In addition, supply grants in the amount of $500 each were awarded to 16 of those awarded fellowships.

The specific areas of research proposed by fellows awarded support during the year numbered 21, and varied from biochemistry to

Analysis of NIH Program Activities

Project Description Sheet

virology. A total of 8 proposed work in neurophysiology; 6 in ophthalmology; and 6 in disorders of the central nervous system.

Significance to Neurological and Sensory Disease research: Because of the complexity of the human nervous system, research in neurological and sensory disorders is especially difficult and often unrewarding. The award of a research fellowship often determines whether an individual can afford to undertake the long and expensive training necessary to competency. Without some source of a continuing supply of scientists primarily interested in fundamental studies the amount of new information to be applied at the clinical level would progressively decrease. This in turn would result in a slowing of progress in solving the problems involved in neurological and sensory disorders.

Proposed course of project: It is proposed to continue this project essentially without change.

12. BUDGET ACTIVITY: Review & Approval

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 OR 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

None providing funds, facilities, or personnel.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE, IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

This program complements the research fellowship program of other Institutes at NIH.

R. P. C. -3
December 1955

Analysis of NIH Program Activities

Project Description Sheet

15. NINDB-EP-2
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

None originating from this office. Grantees, however, publish freely.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

None.

R. P. C. -1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Neurological Diseases and Blindness
INSTITUTE

2. Extramural Programs
LABORATORY OR BRANCH

3. ______
SECTION

4. ______
LOCATION (IF OTHER THAN BETHESDA)

5. NINDB-EP-3
SERIAL NO.

6. Graduate Medical Training Grant Program
PROJECT TITLE

7. Gordon H. Seger, Dr. P. H.
PRINCIPAL INVESTIGATORS

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objective: To increase the number of teachers and clinical investigators competent in the field of neurological and sensory diseases.

Method employed: After careful review by consultant panels chosen especially for competence in medical education, grants are made to training institutions to enable them to establish, expand and improve graduate training programs in neurology, ophthalmology and otology, i.e. the three specialties most directly involved in neurological and sensory disorders. Applications describe in detail the training program proposed, the staff to carry on the training, and training facilities including both inpatient and outpatient arrangements. The length of training varies from two to four years depending on the specialty involved and results in eligibility for AMA certification to follow a career in the specialty for which trained. Funds granted are used primarily for additional staff and trainee stipends.

Analysis of NIH Program Activities

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Major fields of emphasis: During the calendar year 1955, 74 training grants were awarded amounting to $1,445,709 and involving 48 training institutions. 54 of these awards in the amount of $1,016,330 were made for training in the field of neurology, and 20 in the amount of $429,379 for training in the field of ophthalmology.

Significance to Neurological and Sensory Disease research: The lack of more rapid progress in solving the multitude of problems in the fields of neurological and sensory disorders is directly attributable to the critical shortage of competent personnel trained for careers in clinical investigation in these areas. Without such personnel information which continually emerges from fundamental studies cannot be readily applied at the clinical level, and therefore, cannot be measured in terms of solving the medical problems involved.

Proposed course of project: Support to those institutions which have been successful in establishing and maintaining a high caliber program will be continued. In addition, and insofar as funds will allow, other institutions requesting support will be financially aided in establishing, expanding and improving graduate training programs in fields closely related to neurological and sensory diseases.

12. BUDGET ACTIVITY: Review and Approval.

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 OR 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

None providing funds, facilities, or personnel.

R. P. C. -3
December 1955

Analysis of NIH Program Activities

Project Description Sheet

NINDB-EP-3
SERIAL NO.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE, IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

None

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

None originating from this office. Grantees, however, publish freely.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

None

R. P. C. -1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. National Institute of Neurological Diseases and Blindness
INSTITUTE

2. Extramural Programs
LABORATORY OR BRANCH

3. ____________
SECTION

4. ____________
LOCATION (IF OTHER THAN BETHESDA)

5. NINDB-EP-4
SERIAL NO.

6. Graduate Clinical Traineeship Program
PROJECT TITLE

7. Gordon M. Seger, Dr. P. H.
PRINCIPAL INVESTIGATORS

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objective: To encourage highly trained medical personnel of known competence to take additional training to fit them for careers in highly specialized areas of clinical investigation.

Method employed: Applications, including supplementary information obtained from former employers and teachers, and transcripts of previous training records are carefully reviewed to evaluate competence and to appraise general potentiality for clinical investigation. Two types of awards are made, the regular traineeship, carrying an annual stipend varying from $3400 to about $4200, depending on the number of dependents, and the special traineeship, for those of unusual competence in which case the stipend is determined by the particular needs of the applicant.

Awards are made in general to candidates who have already completed the requirements for specialty certification and desire additional training in the neurological or sensory field

Analysis of NIH Program Activities

Project Description Sheet

to apply to their work in their chosen specialty. Common examples are pediatricians who desire additional training in pediatric neurology, ophthalmologists desiring training in ocular pathology, internists seeking a year's training in clinical neurology, neurologists who wish additional training in neurophysiology, etc.

Major fields of emphasis: During the calendar year 1955, 52 clinical traineeships were awarded for training at 27 training institutions in the United States and 1 foreign institution. 26 of these awards were for special training in clinical neurology; 19 in ophthalmology; 3 in neurosurgery; 2 in neuropathology; 1 in neurophysiology and 1 in rehabilitation.

Significance to Neurological and Sensory Disease research: The value of highly trained clinical investigators in a field that presents as many complex problems as does the area of neurological and sensory disorders cannot be overemphasized. It is from such specialists that leadership in the field is most commonly found and from which important contributions in clinical research frequently emanate.

Proposed course of project: It is proposed to continue this program with emphasis on but not limited to those applicants from specialties not covered in the Graduate Medical Training program, in order that this program may complement the larger effort to provide competent clinical investigators.

R. P. C. -3
December 1955

Analysis of NIH Program Activities

Project Description Sheet

10. NINDB-EP-4
SERIAL NO.

12. BUDGET ACTIVITY: Review and Approval

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 OR 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

None providing funds, facilities, or personnel.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE, IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

None

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

None originating from this office, Grantees, however, publish freely.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

None

National Institute of Neurological Diseases and Blindness

Clinical Investigations Annual Report

The Clinical Director's Report

General:

At the time of submission of the third annual report, the Clinical Investigation Unit of the National Institute of Neurological Diseases and Blindness has reached its total activation of three wards for a total of 78 beds. There were 357 in-patient admissions and 548 outpatient admissions. With the addition of Doctor Ludwig von Sallmann, the Branch of Ophthalmological Disorders rapidly expanded with the activation of six sections, recruitment of 13 investigators, and their supporting staff of technicians, etc. A corresponding increase in the number of research projects since 1954 shows a total of 98 projects for the Clinical Investigation Unit of this Institute. Many and varied neurological and ophthalmological diseases are under investigation with both clinical and applied basic research in such areas. Neurosurgery has been occupied with continuing studies of brain physiology and its relation to epilepsy, and, in particular, to seizures originating in the temporal lobe and the deep nuclei of the temporal lobe. In addition, studies in involuntary movement, pain, and the effects of surgical removals on the visual system have received intensive investigation. The Medical Neurology Branch is still continuing its studies on diseases of the lower motor neuron, demyelinizing disorders, amyotrophic lateral sclerosis, and other diseases of the central and peripheral nervous system. The new Ophthalmological Branch has launched a broad program into the cause and basic mechanism underlying glaucoma, cataract, and inflammatory diseases of the orbit. The Epidemiology Branch has continued its field studies on amyotrophic lateral sclerosis and a pilot study of all neurological diseases in small closed medical communities. The Electroencephalography Branch has carried on studies of the correlation of metrazol-induced seizures, and the correlation of such with clinical and pathological material. This Branch is continuing its studies of experimental seizures utilizing injected penicillin and its studies on the thalamic and cortical connections.

Specific:

The Medical Branch, in its studies on neuromuscular disorders, has completed, with the aid of Doctor J. Godwin Greenfield, a basic Atlas of Muscle Pathology which has been accepted for publication by E. & S. Livingstone in Edinburgh, England. This pathology is based on approximately 5,000 slides from biopsies obtained from 127 patients with neuromuscular disorders. Specific pathological changes are described in afflicted muscle fibers and the nuclei. Positive and negative clinical correlation have been presented in tabular form to demonstrate the basic pathology of neuropathies and myopathies. Regeneration of muscle has been demonstrated in patients with muscular dystrophy, and specific anatomical pathological changes are illustrated in dystrophia myotonica, but it has been found that it is impossible to differentiate muscular dystrophy from polymyositis on the basis of pathology alone.

Patients with muscular dystrophy have shown a decreased exchange of body potassium. Such an exchange, however, is a reflection of the decreased muscle mass of the body and not an inability of the muscle cell to use potassium. Dystrophic patients show an abnormal permeability to albumin tagged with Iodine 131. Such a permeability does not exist if the tag is on the red cell with Chromium 51. It is still not clear whether the protein is fractionated before or after leaving the blood stream. Studies in this regard are continuing. The finding of larger than normal amounts of oxyproteic acid in the urine of dystrophic patients by Doctor Curtis again points to some abnormality in protein metabolism.

The main emphasis of this Branch will now turn to the disease myasthenia gravis. It has been found that hexamethonium will relieve in part the symptoms of myasthenia gravis. Hexamethonium will also reverse the paralysis of the rat receiving either decamethonium or curare. The way in which this is done is not clear since hexamethonium presumably has no anticholinesterase activity. To further elucidate this, as well as the physiology of the altered end plate in myasthenia gravis, Doctors Shy and Li have been attempting to record from a single motor end plate while within a muscle fiber. They have been aided in this regard by Doctor Paul Fatt from Australia, and single end plate potentials have now been recorded for the first time _in vivo_ from the mamalian muscle.

Doctor Tower and his group have demonstrated quantitatively an increase in aldo pentose excretion in patients with neuromuscular disease, but this also seems a reflection of the residual muscle mass and not of primary etiology in the disorder of muscular dystrophy. Doctor Horvath and Doctor Shy are continuing the studies of actomyosin threads and glycerinated fibers in muscle diseases. It would appear that normal human muscle is extremely sensitive to changes in ATP, potassium, and magnesium. Myotonic muscle, however, will contract over a broad spectrum of concentrations of these substances.

Doctor Tower and his group are continuing their studies of changes accompanying demyelinizing disorders that confirm Kabot's findings that 65% of patients with multiple sclerosis demonstrate an increase in gamma globulin. Such an elevation, however, rarely proceeds an onset of symptoms. Electrophoresis studies further reveal that an increase in gamma globulin occurs in many neurological disorders, with higher levels found in the cerebellar ataxias, all of which discredits the specificity of gamma globulin in the diagnosis and prognosis of multiple sclerosis. A double-blind pilot study involving 81 patients with reference to the effectiveness of isoniazid was carried out concomitantly with the above studies. It was concluded that acute exacerbations were not prevented by isoniazid and that the therapeutic effect of isoniazid remained to be proved.

Doctor Tower's group is continuing its studies into the epileptic cortex and glutamic acid synthesis with the utilization of carbon 14 labeled asparagine. A new method for isolation of amino acids in the spinal fluid by changing them to their dinitrophenyl derivatives and subsequent separation by column chromatography has been developed in Doctor Tower's and Doctor Curtis' laboratories. Similar studies with aspartic acid and gamma aminobutric acid are underway. In their studies as to the clinical effects of glutamine and asparagine on generalized seizures, Doctors Tower and Wells have surveyed 45 patients, of which 23 remained on medication. Three examples of toxicity manifested by nausea and vomiting were noted. In addition to decrease of seizures, an increase in alertness and well-being was noted in the 23 remaining patients. They hope to continue their studies utilizing also enterically-coated alpha-ketoglutarate. Quantitation of the amount of these substances in the cerebro-spinal fluid plasma is proceeding.

Doctors Wells and Tower are combining with Doctor Sokoloff in the studies of the effect of ventilation in "petit mal" seizures by use of Kety's radioactive krypton^{79} method. Doctors Wells, Tower, and Haase are studying the concentration of B-12 in the spinal fluid. Doctor Tower is to be a co-author of a book of neurological chemistry to be published within the next year.

Doctor Chatfield is continuing his studies of temperature and its effect on the myoneural junction. He finds the lower temperatures at lower frequencies will initiate tetanus in hamster muscle. He finds but little relationship to the amplitude to muscle response and the tension developed. Doctor Chatfield has finished a book on clinical neurophysiology which will be published by Charles C. Thomas and Company.

Doctor Irwin and Mr. Wells have continued their studies despite the protracted illness of Doctor Irwin. They have carried on studies in the cross transfused head technique in relationship to respiratory and vasomotor response to central nervous system asphyxia. They find that the anterior spinal artery of the dog may carry enough blood flow to keep such centers functioning when all other blood supply is eliminated. They are continuing their studies in calcium metabolism in relation to neuromuscular blocking agents. They find calcium antagonistic to succinyl choline and that this antagonism is independent of adrenalin release and occurs in the presence of acidemia during hyperpnea.

Under the direction of Doctor Baldwin and his group, studies in the physiology of the cortex and its deep nuclei are continuing with utilization of patients with focal seizures, in particular, the temporal lobe. It would appear that patients with temporal lobe lesions have primary difficulty in awareness, attention, and perceptual analysis. Four patients yielded distinct memory patterns on stimulation of the temporal lobe. Studies are underway to isolate the vestibular isolation in the temporal lobe and initial studies seem to indicate that nystagmus can be illicited only in posterior temporal sections. Stimulation of the amygdaloid nucleus has given rise to motor and postural changes, in particular, in the face and upper extremity. The most consistent change in the amygdaloid stimulation is loss of consciousness. A variety of autonomic effects are being recorded both in man and higher primates in the amygdala and insula. Secondary sensory areas have been found to extend in the island of Reil and in the first and second temporal gyrus. Changes in blood pressure, pulse, temperature, and gastric mobility have been recorded in stimulations of the island of Reil. A new apparatus has been prepared to stimulate peripherally for recording evoked potentials on the cortex. Apparently difficulty in speech may arise from lesions in either temporal lobe, the dominant temporal lobe being more aphasic in character and the less dominant having difficulty in the handling of semantics. There seems to be a direct relationship between psychotic episodes and epileptiform activity in the temporal lobe in the majority of patients. Stimulation of the deep nuclei of the temporal lobe in higher primates shows first a widening of the palpebral fissure, a dilation of the pupil on the side of stimulation, the salivation, and, finally, the posturing characteristic of this area.

Doctor Frost and his section seems to feel that memory per se is not necessarily affected in temporal lobe lesions in both man and primates but that the main difficulty seems to lie in the attention and concentration, and, in particular, to perceptual relationships to other individuals. The Psychology Section is also initiating a long-term study in the affects of anti-epileptic agents on intelligence. A study of tissue removed at cortical surgery seems to reveal at least five types of lesions: 1) a pseudolaminar necrosis; 2) complete cortical necrosis; 3) a deposition of a peculiar type of lipid that stains with Sudan IV but also with thionine and is not dissolved in paraffin preparations. The other two changes found at pathology are neuronal damage with astrocytosis and meningo-cerebral cicatrix. Surgical studies for the relief of pain are continuing, utilizing the polygraphic analysis of patient response.

Much time has been spent in the Branch of Surgical Neurology in further elucidating neuro-ophthalmological pathways and their pathology. Attempts have been made to plot ganglionic changes in the retina from pregeniculate lesions with considerable success by

Doctor Van Buren. Studies are continuing into the primary pathology of papilledema in which characteristic swelling of the nerve endings have been seen on the retinal side of the lamina cribosa. Such swellings separate the lamina cribosa from Bruch's membrane and the fibers are caught in a sharp angulation around Bruch's membrane and it can be seen that this might well permanently damage the optic fibers. The characteristic visual field of a temporal lobe lesion is not homonymous and the effects are larger and more dense ipsolateral to the lesion. Lesions in the temporal lobe do not extend in their retrograde regeneration to all six layers of the lateral geniculate and it is suggested that perhaps macular fibers lie deeper in the geniculate. The first case of human moniliasis in the eye is being reported by Doctor Van Buren.

The Section of Neuropathology has recently lost its chief and recruitment for a new head of this Section is in progress. Doctors Alvord and Brace have finished their studies of x-ray induced lesions of the central nervous system and have reported this in London, England, under the title "X-Ray Induced Pyknosis of Cerebellar Granule Cells in Guinea Pigs." They have shown considerable protection to radiation by pre-administered nembutal. Doctors Alvord and Goldstein of the Institute of Mental Health have continued their studies on artificial demyelinization using some 450 animals. That portion of the brain homogenate that seems responsible has been isolated to a water soluable product. Doctor Alvord and Doctor Whitlock have finished their work on the startle response and, in particular, to the necessity of the sensory-motor area to startle response under light chloralose.

Doctor Li has extended over the past year his studies utilizing micro-electrodes of less than one-half micron in diameter. Such studies are being carried out in the human operating room as well as in the primate operating room. The functional properties of cortical neurons with particular reference to strychnine as well as the effect of recording responses of evoked neuronal discharges are under study. More recently Doctor Li, by this technique, has demonstrated that the nucleus ventralis lateralis has an inhibitory effect on the premotor cortex.

Doctor von Sallmann is continuing his studies that he started before joining the Institute of a systematic exploration of thalamic and hypothalamic nuclei and their effect on ocular pressure. He had previously reported an increase of intraocular pressure on stimulation of the ventral thalamus and dorsal hypothalamus. He now finds an increased ocular pressure on stimulation of the posterior hypothalamus and medial ventral thalamus. Accompanying this is a rise in the subscleral temperature. He has ruled out the cervical sympathetics and the external ocular muscles as a cause for the increased pressure. Occlusion of the internal carotid artery will drop this pressure but it will rapidly return to its preocclusion height. It is abolished by the drugs Priscoline and Thorazine. Since general body functions such as blood pressure and pulse have effects on internal ocular pressure, the Branch of Ophthalmology has devised a multichannel transducor apparatus to try and exclude as many of these factors as possible. The external ocular muscles will be excluded by electromyographic techniques. Studies as to the peripheral receptors responsible for internal ocular pressure are being undertaken in reference to the innervation of the anterior chamber with particular reference to the trabecular network and its relation to Schlemm's canal.

Studies in the origin of cataracts by ionizing radiation, diet, and drugs constitute another large project in the Branch of Ophthalmology. Galactose cataracts are being studied in which particular emphasis has been placed on the histology of whole lens mounts. Apparently changes in the lens epithelium and the peripheral fibers proceed the actual degeneration in the lens and both proceed opacities. The feeding of myleran or the withholding of tryptophane from the animal will also precipitate such cataracts and these two methods will be used in future studies. In the studies of ionization changes in the lens, the mitotic index of the lens epithelium may be used as an index of radiosensitivity. Such an index is apparently the highest in the monkey. The ionization changes in the lens are remarkably similar to the degeneration with age and may be of value to the study of senile cataracts. Doctor O'Rourke and his group are studying the effects of steroids in uveitis. Horse serum may readily precipitate uveitis. The extent of the uveitis may be determined by four criteria: 1) keratitic precipitates; 2) aqueous cellularity; 3) aqueous beam; 4) iris hyperemia. Using such criteria values, steroidal drugs may be tested. It has been found that one-fifth a dose of prednisone is necessary to equal that of the other corticoids. However, ultimate clearing of this uveitis is not shortened by such a drug. Side effects, however, are less with such lower doses. Doctor O'Rourke is continuing his studies on ocular melanoma and is closely associated with the instrument development section of the Oak Ridge Laboratories. His primary interest is to differentiate ocular melanoma from other intraocular tumors. A collimated scintillation counter has been developed to aid in this study and a strain of mice are utilized in which an S-91 malignant melanoma has been induced. The amount of escape of P-32 in external ocular muscles, scleral tissues, and in the globe will be studied. Doctor Bornschein, Doctor Wanco, and Doctor Iser are continuing studies on the electroretinogram, and, in particular, the effects of photic stimulation in the rise rate to study accomodation in the optic nerve. They are also studying hypothermia on the electroretinogram and controlling their temperature evaluation from the cheek-pouch. Doctor Tanaka and Doctor O'Connor are continuing their studies of inflammatory diseases of the eye, in particular, trachoma and the E.K.C. virus. The finding that the A.P.C. virus may grow on conjunctival epithelial cultures may do much to aid the study of trachoma. Labeled antibodies are being utilized to study the predilection to ocular toxoplasmosis. Doctor Gunkel is continuing his instrument development section and is further refining his magnetic self-recording screen and methods for better evaluation of flicker fusion fields. Doctor Resnik and his staff are now studying the proteins of the lens by fractionation through a base ion exchange resin and then further separation by ultracentrifuge and electrophoresis. Doctor Resnik has finished his study on alloxan and showed that it does not form a complex with metals as previously determined.

Doctor Kurland in the past year has continued his studies in amyotrophic lateral sclerosis. In an attempt to differentiate genetic from environmental factors, he carried on a study among the Chamorro's in California who migrated from Guam. It is Doctor Kurland's initial opinion that the incidence among the Chamorros will be as high as in their families back home. Doctor Kurland, in addition, went to Europe to the Archivo de Indias in Seville, Spain and to the records of the Jesuits in the Vatican Library. All the early references he could locate indicated that they were a healthy and long-lived group so his impression that amyotrophic lateral sclerosis was introduced by the Spaniards had been strengthened. This was further supported by the possibility that one of the Spanish islands off the mainland had an incidence much above normal. At the present Doctor Kurland is working in the Armed Forces Institute of Pathology where he is reviewing the cases of amyotrophic lateral sclerosis and related disorders to further understand such disease and in hopes of finding some lead to direct his search for the hypothetical underlying metabolic defect.

Doctor Ajmone Marsan, in addition to his heavy clinical responsibilities, has carried out, along with Doctor Ralston, a clinical electroencephalographic correlation of metrazol-induced seizure patterns. The MIS faithfully reproduced the patients' attack pattern in 85% of the cases and in 90% of the spontaneous attacks observed while off medication. Motor lateralizing signs are present in an unexpectedly high number of temporal cases. While visceral or non-visceral automatisms may be found in sites other than the temporal lobe, if the attack consists of automatisms alone the EEG is strikingly characterized by lack of changes or by unitemporal activation. If there is automatism plus aphasia, the EEG changes are usually bilateral temporal. Other correlations can be noted in project number 91. Doctor Ajmone Marsan is continuing his investigations in animals and the recruiting response in cortical and subcortical structures. He finds a progressive activation of two elements differing by the number of synapses, waning indicates a drop out of neurons of the shortest path. The recording of nonspecific responses from a surface cortical electrode and from electrodes at different levels from within the cortex and underlying white matter and basal ganglia with a similar latency but with recruitment and waxing and waning seems to indicate that such events must occur within the thalamus. Doctor Ralston and Doctor Ajmone Marsan are studying the effects of locally applied penicillin to the thalamic nuclei and the projection of the abnormal response. They also find that penicillin placed in the mesial thalamus and cingulate gyrus activates the spindle response.

With the calling together of scientists throughout the Country interested in cerebral palsy, Doctor Bailey has initiated a broad research program in this relatively little understood field. A preliminary protocol was formulated by this Committee which will guide the efforts of both intramural and extramural research teams. Most of the pathological material will ultimately pass through the National Institute of Neurological Diseases and Blindness where it will be reviewed by Doctor Anatole Dekaban, who has recently joined the Institute. Doctor Dekaban has, in addition, initiated a large pre- and post-natal study in cooperation with the Army and Navy Centers of Washington, with reference to various factors that may induce cerebral palsy. He is, in addition, working on the embryology of the mouse brain in anticipation of studying the effects of radiation at various stages of fetal growth and their correlation with lesions of the central nervous system. The Cerebral Palsy Program intramurally has been further strengthened by the addition of a pediatric neurologist, Doctor Gordon Millichap, who has been studying the effects of relaxant drugs on involuntary movements and rigidity. He finds initially that both may be increased with Reserpine or decreased with Flexin (2-amino-5-chloro-benzoxazole). In addition, he is studying the effects of carbonic anhydrase inhibitors on the cerebral seizures of childhood. He has initiated a study of the incidence of precocious puberty in cerebral palsied children.

These, then, are some of the specific studies that have been undertaken by the Clinical Investigation Unit of the National Institute of Neurological Diseases and Blindness. 39 manuscripts have been prepared or have been published during the past year, and 3 books are in the process of publication.

G. Milton Shy

G. Milton Shy, M. D.

CLINICAL INVESTIGATION UNIT

PUBLICATIONS - 42

	Manuscripts	Books	Total
MEDICAL NEUROLOGY BRANCH:			17
Neurological Disorders	6	2*	
Neurochemistry	7		
Neurophysiology	1	1	
SURGICAL NEUROLOGY BRANCH:			11
Neurosurgical Disorders	5		
Neuropathology	1		
Experimental Neurosurgery	5		
CEREBRAL PALSY:	2		2
OPHTHALMOLOGY:	6		6
ELECTROENCEPHALOGRAPHY:	1		1
EPIDEMIOLOGY:	5		5
	39	3	42

* Contributors from Surgical Neurology and Basic Research Unit.

TABLE I

Table of Organization of Clinical Investigations Personnel

(Personnel On Hand December, 1955)

Office of Clinical Director:

Clinical Director -- Dr. G. Milton Shy, M.D., M.S., M.R.C.P.

Administrative Assistant -- Mr. Elliot Brookman, B.A.

Secretary -- Mrs. Catherine Thomas

Secretary -- Mrs. Rae Myers

Branch of Medical Neurology: Dr. G. Milton Shy, Acting Chief

Neurological Disorders Service:

Clinical Associate -- Dr. Gunter Haase, M.D.

Clinical Associate -- Dr. Kenneth Magee, M.D.

Clinical Associate -- Dr. Glenn Drager, M.D.

Visiting Scientist -- Dr. J. G. Millichap, M.D.

Secretary -- Mrs. Aileen Poole

Secretary -- Miss Joyce Jenkins

Physical Science Aid -- Mr. William Matthews

Clinical Neurophysiology Section:

Neurophysiologist -- Dr. Paul Chatfield, M.D., Chief

Secretary -- Miss Dorothy Haase

Physical Science Aid -- Mr. Jeu S. Ming

Biophysical Applications Section:

Acting Chief -- Dr. G. Milton Shy, M.D., M.S., M.R.C.P.

Clinical Applied Pharmacology Section:

Pharmacologist -- Dr. Richard Irwin, Ph.D., Chief

Physiologist -- Mr. Jay B. Wells

Clerk-Typist -- Miss Alice Louise Cecil

Clinical Neurochemistry Section:

Neurochemist -- Dr. Donald Tower, M.D., Chief
Muscle Chemist -- Dr. Beni Horvath, M.D., Ph.D.
Chemist -- Dr. William Curtis, Ph.D.
Physical Science Aid -- Mr. John Phoenix
Physical Science Aid -- Mr. Edmund Peters
Clerk-Stenographer -- Mrs. Virginia Gray
Physical Science Aid -- Mr. Joseph Proctor
Research Associate -- Dr. Charles Wells, M.D.

Surgical Neurology Branch: Dr. Maitland Baldwin, Chief

Neurosurgical Disorders Service:

Neurosurgeon -- Dr. Maitland Baldwin, M.D., M.S., F.R.C.S., Chief
Neurosurgeon -- Dr. John Van Buren, M.D., M.Sc.
Neurosurgeon -- Dr. Edward Laskowski, M.D.
Clinical Associate -- Dr. William Headley, M.D.
Nurse -- Miss Karma Eastman
Secretary -- Miss Florence E. Beyer
Clerk-Stenographer -- Mrs. Maxine Reynolds
Clerk-Stenographer -- Mrs. Florence Heller
Supv. Histopath. Technician -- Mr. Fred Meiller

Experimental Neurosurgery Section:

Neurosurgeon -- Dr. Choh-luh Li, M.D., Chief
Med Bio Tech -- Mr. Alan Rowe
Physical Science Aid -- Mr. Phillip McGrath
Physical Science Aid -- Mr. Clarence Gilkes
Physical Science Aid -- Mr. Ulysses Robinson
Lab Animal Caretaker -- Mr. Otis Prince
Med Bio Tech -- Mr. Norman Mills
Animal Caretaker -- Mr. George Duvall

Experimental Neurosurgery Section (Cont.):

Med Bio Tech -- Mr. James Burch

Clerk-Stenographer -- Miss Vera Douglas

Nurse -- Miss Shirley Lewis

Clinical Psychology Section:

Psychologist -- Dr. Laurence Frost, Ph.D.

Psychologist -- Miss Mildred Blevins

Clinical Neuropathology Section:

Acting Chief -- Dr. John Van Buren, M.D., M.Sc.

Histopathology Technician -- Mrs. Gladys Moore

Histopathology Technician -- Mr. Daniel Williams

Histopathology Technician -- Mr. Eustace Bourne

Clerk-Stenographer -- Mrs. Mary Di Pietro

Section on Embryological Neuropathology:

Embryologist -- Dr. Anatole Dekaban, M.D.

Histopathology Technician -- Miss Marie Kendall

Clerk-Stenographer -- Mrs. Grace Moore

Ophthalmology Branch:

Chief -- Dr. Ludwig von Sallmann, M.D.

Secretary -- Mrs. Frances Dearman

Clerk-Stenographer -- Mrs. Delma Snouffer

Clerk-Stenographer -- Mrs. Rose Daniele

Ophthalmological Disorders Service:

Clinical Associate -- Dr. James O'Rourke, M.D., Chief

Clinical Associate -- Dr. Gilbert Iser, M.D.

Clinical Associate -- Dr. George Goodman, M.D.

Clinical Associate -- Dr. Monte Holland, M.D.

Clinical Associate -- Dr. George O'Connor, M.D.

Ophthalmological Disorders Service (Cont.):

Clerk-Typist -- Mrs. Harriett Murphy

Ophthalmology Pharmacology Section:

Pharmacologist -- Dr. Frank Macri, Ph.D., Chief

Ophthalmology Physiology Section:

Visiting Scientist -- Dr. Hans Bornschein, M.D.

Visiting Scientist -- Dr. Theodo Wanko, M.D.

Physicist -- Dr. Ralph Gunkel, O.D.

Chemist -- Miss Patricia Grimes

Physical Science Aid -- Mr. Humphrey Patton

Ophthalmology Chemistry Section:

Chemist -- Dr. Robert Resnik, Ph.D., Chief

Chemist -- Mrs. Ann Wolff

Chemist -- Mr. Frank Suggs

Ophthalmology Bacteriology Section:

Visiting Scientist -- Dr. Chie Tanaka, M.D.

Bacteriologist -- Miss Mary Jane Cook

Physical Science Aid -- Mr. James Mitchell

Ophthalmology Histopathology Section:

Physiologist -- Mr. Leo Caravaggio

Histopathology Technician -- Mrs. Eleanor Collins

Branch of Electroencephalography:

Chief -- Dr. Cosimo Ajmone-Marsan, M.D., Ph.D.

Research Associate -- Dr. Bruce Ralston, M.D.

Technician -- Miss Maureen Benson

Technician -- Miss Carol Caswell

Technician -- Miss Helen Torrence

Secretary -- Mrs. George Ann Johnson

Physical Science Aid -- Mr. Samuel Cooper

Epidemiology Branch:

Epidemiologist -- Dr. Leonard Kurland, M.D., Chief

Clerk -- Miss Mary Kay

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Medical Neurology
BRANCH

3. Neurological Disorders Service
SECTION

4. -
LOCATION

5. NINDB-1 (C)
SERIAL NO.

6. Studies in the Pharmacology of Myasthenia Gravis and Studies in Prostigmine Tolerance
PROJECT TITLE

7. G. Milton Shy, M. D.
PRINCIPAL INVESTIGATOR

8. L. P. Rowland, M. D., Leonard Berg, M. D. and Richard L. Irwin, Ph.D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective: In the treatment of myasthenia gravis, one item of essential information has long been lacking, and to a certain extent, a matter of controversy. It is known that in many myasthenics assistance cannot be afforded by large amounts of prostigmine, and, in others, symptoms may become so severe that the patient dies despite the administration of large amounts of this drug, which is presumably almost specific treatment for the disease. It has been the opinion of some investigators that this occurs merely because the patients are receiving an insufficient amount of prostigmine. Others have held the opinion that the patients are actually refractory to the drug; and some have feared to give large amounts of the drug because of possible adverse affects on muscle strength; i.e., the patient might become weaker rather than stronger. Because critical data on this problem are lacking, the following investigation is contemplated and underway.

Method employed: To myasthenic patients with varying degrees of severity of the disease, injections of prostigmine are given over a period of several hours. At first, only small amounts are used and this is gradually increased. This is continued until the patient achieves an optimal response in terms of increased strength. Concomitantly the likelihood for annoying side effects are observed. At this point, the injection is gradually increased to see how long the optimal state can be maintained and what happens beyond this point. Correlated with this study are measurements of serum cholinesterase and evaluation of the response of muscle to nerve stimulation.

R.P.C. 1 (a)
December, 1955

NINDB-1 (C)
SERIAL NO.

Patient Material:

		No.	Avg. Stay Days
Admissions:	Adult males	2	23
	Adult females	4	135.8
	Children males	-	
	Children females	-	
Outpatients:	Number of patients	0	
	Number of visits	0	

Major findings: Recently this group of investigators have attempted to correlate all known information on myasthenia gravis into a plausible scheme and to attempt animal experimentation and subsequent human experimentation to demonstrate the plausibility of this scheme. If one searches for a depolarizing type of agent such as decamethonium in the myasthenic patient instead of nondepolarizing agent such as curare, then all research work in myasthenia gravis can be fitted into one scheme. Repetitive dosages of decamethonium will change the block from a depolarizing type of block to a competitive block. Some muscles are more sensitive to this than are others and those are primarily the muscles affected in myasthenia gravis. In muscles not so affected, however, an increased tolerance to decamethonium occurs as has been demonstrated by Churchill-Davidson in England, whereas those muscles affected to the point that a competitive block exists will become worse. It would be at this stage that myasthenia gravis would present. At this stage prostigmine will reverse the competitive block and we have done such in the laboratory. If one increases the competitive block to the point that only 5% of the twitch potential remains, then prostigmine or tensilon will not reverse this block. However, results in this laboratory demonstrate that hexamethonium will. At the point at which a depolarizing blockade becomes a competitive blockade, tetanus will no longer be held and will increase the blockade as shown in this laboratory. Curare itself acts as a competitive blockade. Further studies, then, must show if hexamethonium will act against curare as well as against decamethonium. If so, this will be the drug of choice in myasthenia gravis. This would also explain why the muscle of a myasthenic not affected by the disease is not resistant to decamethonium while those affected are not susceptible. It will also explain why some myasthenics react at some stages to prostigmine and not to others. Extracts of the thymus also give a blockade which resembles the depolarizing blockade and not a curarizing blockade.

Approximately 35 cats and 62 rats have been studied as to the affects of decamethonium blockade. From these studies it would appear that the decamethonium series rapidly changes from a depolarizing block to a competitive block which is indistinguishable from curare. At this point prostigmine will alleviate either a decamethonium block or a curare block as will hexamethonium.

It is therefore apparent that the only way to solve this problem is direct electrical recording off a single motor end plate and a single muscle fiber. This required complete retooling of the laboratory, which has now been accomplished, and with the aid of Doctor Paul Fatt from England we have been able to record motor end plate potential on the isolated sartorius muscle of the frog, from the muscles of the intact frog, and from the muscles of the intact rat. This has been the first time that motor end plate potentials have been recorded from the intact animal. The next stage will be recording from myasthenic muscle of the human patient.

Significance to neurological research: Primary studies on a few patients indicated that in some patients, at least, adverse symptoms will appear before myasthenia symptoms can be completely relieved, even when an attempt is made to control these side effects by the administration of specific antidotes. Among the adverse symptoms which have been noted is the decline in muscle strength, even greater than the weakness prior to the administration of prostigmine. If further study can corroborate these findings or further analyze them, that should have significant implications for the treatment of the disease and may cast some light on the nature of the disease.

Direct electrical recording from the motor end plate and its muscle fiber will be the only way that direct evidence may be found for a competitive or depolarizing substance in the myasthenic patient.

Proposed course of the project: This project will become the major research effort of the medical branch of this Institute in the coming year, and beds will be made available for myasthenia gravis patients if the initial studies are successful.

R.P.C. 2
December 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB-1 (C)
SERIAL NO.

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11. BUDGET DATA:

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12. BUDGET ACTIVITY: RESEARCH

13. NONE.

14. NONE.

Honors, Awards, and Publications

16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

Rowland, L.P., Korengold, M.C., Jaffe, I.A., Berg, L. and Shy, G. M. Prostigmine-Induced muscle weakness in myasthenia gravis patients.
Neurology, Vol. 5, No. 2, February, 1955.

Rowland, Lewis P.
Prostigmin-responsiveness and the diagnosis of myasthenia gravis.
Neurology, Vol. 5, No. 9, September, 1955.

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17. HONORS AND AWARDS TO PERSONNEL DURING 1955:

None

R.P.C. 1
December 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Medical Neurology
BRANCH

3. Neurological Disorders Service
SECTION

4. ________
LOCATION

5. NINDB-2 (C)
SERIAL NO.

6. Ionic Exchange in Neuromuscular Disease
PROJECT TITLE

7. G. Milton Shy, M. D.
PRINCIPAL INVESTIGATOR

8. Beni Horvath, M. D., Leonard Berg, M. D., and Donald Cummings
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objective: Proposed plan to determine the effect of potassium metabolism, in particular, intracellular concentrations of potassium in neuromuscular disorders, by the use of tracer elements and flame photometry and the utilization of specific pharmacological agents.

Method Employed: Clinical material will be subjects with muscular dystrophy, myasthenia gravis, myotonia, and myositis. Biopsies will be removed from such subjects under major nerve block. Our modification of the Boyle-Conway technique will be used for extracellular space. This procedure will continue to be controlled by conscientious objectors. Animal experimentation will be continued in rabbits, rats and guinea pigs, the experimentation on goats having now been terminated.

Patient Material:

		No.	Avg. Stay Days
Admissions:	Adult males	11	31.3
	Adult females	5	38
	Children male	7	30.9
	Children females	0	
Outpatient:	Number of patients	0	
	Number of visits	-	

Major Findings: Within the last year this unit has established a technique whereby the sodium and potassium of residual muscle and the amount of potassium exchanged in residual muscle can be determined in various diseases. In muscular dystrophy it has been demonstrated that potassium is low and sodium is high, and a regression curve may be drawn between the two. In spite of this, however, the potassium turnover of microcuries per milliequivalent

9. PROJECT DESCRIPTION (Continued)

is within the range of normal demonstrating this result to be the effect and not the cause of the disease. In myasthenia gravis this technique has been utilized to demonstrate that the defect in potassium lies in an inability to enter the cell or an excess leakage from the cell. The first has been related to the anticholine esterase group of drugs and the second to the choline acetylase system. Initial results of this were reported at the Myasthenia Gravis Foundation Conference.

1) Residual muscle tissue of patients with muscular dystrophy contains an elevated sodium and reduced potassium concentration. Such concentrations may be correlated with the decrease of residual fiber water. There is a significant correlation between the lowering of the potassium concentration and the elevation of the sodium concentration.

2) The utilization of iodinated albumin demonstrates that the dystrophic patient either fractionates protein within his blood vessels or abnormally fractionates it from a vessel whose permeability is increased. Thus, the dystrophic patient may show concentrations up to 50% by using iodinated albumin, whereas such concentrations will be 8 to 10% when Chromium 51 tagged red cells are used. Since the same muscle that shows 50% vascularity with iodinated albumin shows but 10 meqs. of potassium per kg., this in reality then could not be explained on increasing vascularity since blood alone would furnish 25 meqs. of potassium. Further studies to find what happens to protein in muscular dystrophy are being carried out.

3) A method is described for the measurement of the amount of potassium exchanged in 22 hours in the whole human body. A procedure is presented to estimate the rate of potassium turnover in human muscle. By using the first of these methods muscular dystrophy patients appear to turn over less potassium in 22 hours than control subjects. The index of the potassium turnover of the muscle as measured by the second method is independent of the amount of potassium exchanged in 22 hours in the whole body. The index of potassium exchanged in dystrophic muscle is in the same range as normal muscle.

Significance to Neurological Research: It is anticipated that the role of potassium exchange is much more important to the general problem of myasthenia, myotonia and muscle wasting than the individual analysis of the potassium level of serum or urine at any one time. The relationship extends to the field of endocrine and metabolic disorders as well as specific neuromuscular disorders.

Proposed course of project: No more studies of ionic concentration or ionic exchange are contemplated. Further studies of the fate of injected protein in dystrophic patients will be carried out.

R.P.C. 2
December 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB-2 (C)
SERIAL NO.

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11. BUDGET DATA:

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12. BUDGET ACTIVITY: RESEARCH.

13. NONE.

14. NONE.

Honors, Awards, and Publications

16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

Horvath, B., Berg, L., Cummings, D. J., and Shy, G. M.
Muscular Dystrophy. Cation Concentrations in Residual Muscle.
J. of Applied Physiology, Vol. 8, No.1, July, 1955.

Berg, L., Ebaugh, F. G., Shy, G. M., Horvath, B. and
Cummings, D. J. Muscular Dystrophy. Blood Content of
Dystrophic Muscles.
J. of Applied Physiology, Vol. 8, No. 1, July, 1955.

Shy, G. M., Cummings, D. J., Berg, L. and Horvath, B.
Muscular Dystrophy. Potassium Exchange in Residual Muscle.
J. of Applied Physiology, Vol. 8, No. 1, July, 1955.

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17. HONORS AND AWARDS TO PERSONNEL DURING 1955:

None

R.P.C. 1
December 1955

Analysis of NIH Program Activities

Project Description

1. Neurology
INSTITUTE

2. Medical Neurology
LABORATORY OR BRANCH

3. Neurological Disorders Service
SECTION

4.
LOCATION

5. NINDB-3 (C)
SERIAL NO.

6. An Investigation of the Relationship Between Blood and Spinal Fluid Glucose.
PROJECT TITLE

7. Leonard Berg, M. D.
PRINCIPAL INVESTIGATOR

8. G. M. Shy, M. D. and Donald Cummings
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Project: An investigation of the relationship between blood and spinal fluid glucose.

Objectives: 1. Elucidation of mechanisms of glucose transfer across blood-fluid barriers, of glucose utilization in brain and spinal fluid in normal and disease states.
2. Elucidation of details of cerebrospinal fluid function.

Methods Employed: The quantity of glucose and its degradation products in the spinal fluid will be followed during experimentally produced changes in the blood glucose. Experiments will be performed on suitable laboratory animals in their normal state as well as during various kinds of meningitis. A new experimental method, namely the use of radioactive glucose to follow glucose metabolism of spinal fluid, will be introduced after preliminary utilizing non-radioactive techniques.

Major Findings: Methods have been developed for the identification, elimination and isolation of glucose in plasma and spinal fluid. Isolation of the compound was necessary primary to the tracing of radioactive glucose because of the obvious necessity of separating the parent compound from radioactive degradation products for counting purposes. Thus far the work has been confined to in vitro experiments. The methods and yields appear to be satisfactory.

Significance to Neurology Research: It is expected that information will be gained relative to general problems of cerebrospinal fluid physiology. Advances in knowledge about mechanisms and treatment of meningitis and hydrocephalus are goals of this project.

Proposed Course of Project: Terminated because of investigator leaving Institute.

R.P.C. 2
December 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB-3 (C)
SERIAL NO.

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11. BUDGET DATA:

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12. BUDGET ACTIVITY: RESEARCH.

13. NONE.

14. NONE.

Honors, Awards, and Publications

16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

None

17. HONORS AND AWARDS TO PERSONNEL DURING 1955:

None

R.P. C. 1
December 1955

Analysis of NIH Program Activities

Project Description

1. Neurology
INSTITUTE

2. Medical Neurology
LABORATORY OR BRANCH

3. Neurological Disorders Service
SECTION

4. ________
LOCATION

5. NINDB-4 (C)
SERIAL NO.

6. Experimental Reduction of Reflex Activity in Special Disease States
PROJECT TITLE

7. M. C. Korengold, M. D.
PRINCIPAL INVESTIGATOR

8. ________
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Project: Experimental Reduction of Reflex Activity in Special Disease States.

Objectives: To determine response of reflex activity in specially prepared laboratory animals to various drugs in an attempt to achieve a reduction in this activity.

Methods Employed: With the use of suitable laboratory animals, experimental transection procedures are performed. Correlations are to be made between state of their reflex activity as influenced by various neuromuscular blocking agents. Of particular interest will be response to various curare and synthetic curare-like preparations, such as d-tubocurarine, repository tubocurarine, flakedil; succinyl choline, metubine, and syncurine. A study will be made of effects of such medication upon the reflex activity, as well as any associated side reactions involving other areas of the animal.

Major Findings: None.

Significance to Neurological Research: It would be of considerable value to learn more about the use of blocking agents in diseases in which spasticity is a major disability. This would be of value in elucidating further information about the nature of tone and factors that might influence it.

Proposed Course of Project: No change.

R.P.C. 2
December 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB-4 (C)
SERIAL NO.

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11. BUDGET DATA:

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12. BUDGET ACTIVITY: RESEARCH.

13. NONE.

14. NONE.

Honors, Awards, and Publications

16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

None

17. HONORS AND AWARDS TO PERSONNEL DURING 1955:

None

R.P.C. 1
December 1955

Analysis of NIH Program Activities

Project Description

1. Neurology
INSTITUTE

2. Medical Neurology
LABORATORY OR BRANCH

3. Neurological Disorders Service
SECTION

4.
LOCATION

5. NINDB-5 (C)
SERIAL NO.

6. Protein Studies in the Hereditary Ataxias.
PROJECT TITLE

7. M. C. Korengold, M. D.
PRINCIPAL INVESTIGATOR

8. I. Jaffe, M. D. and C. Wells, M. D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Project: Protein studies in the hereditary ataxias.

Objectives: To determine the qualitative and quantitative protein components of the cerebral spinal fluid and their relationship to serum proteins and other examinations of protein normalcy.

Methods Employed: Patients are to be suitably screened in the Out-Patient Department for disease consistent with the diagnosis of Cerebellar Ataxia. These people will then be admitted as in-patients and blood studies consisting of total and fractional proteins, cephalin flocculation, and thymol turbidities will be run. Spinal fluid will be examined for its differential protein content by means of paper electrophoresis. Similar studies will be run on serum by means of paper electrophoresis, so that adequate comparisons can be made on the significance of protein abnormalities appearing in either area.

Patient Material:		No.	Avg. Stay Days
Admissions:	Adult males	6	34.2
	Adult females	2	25
	Children male	1	6
	Children female	-	
Outpatient:	Number of patients	2	
	Number of visits	2	

R.P.C. 1 (a)
Dec. 1955

NINDB-5 (C)
SERIAL NO.

Major findings: Patients with hereditary cerebellar ataxia demonstrate the highest amount of gamma globulin in the spinal fluid that we have as yet determined. Since the presence of an increased gamma globulin in the spinal fluid has been stated to be specific for multiple sclerosis by some medical centers and since the average case of cerebellar ataxia is diagnosed by the uninitiated as multiple sclerosis, it would appear that these findings are of importance in two ways: 1) to show that an increase in gamma globulin is not specific to multiple sclerosis; and, 2) that this is the single neurological disease which gives the largest quantity of gamma globulin. The reason for the latter is not clear and a proposed course of this project will be toward elucidating protein metabolism in this disorder.

Significance to Neurological Research: To assist in learning new information about a system disease that may prove of value in correlating protein abnormalities in this condition with chemical abnormalities found in other demyelinizing states. This may lead to previously undescribed abnormalities that may be of value in better understanding the nature of this disease and assist in providing a clue for possible future therapy.

Proposed Course of Project: A proposed course of this project will be toward elucidating protein metabolism in this disorder.

R.P.C. 2
December 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB-5 (C)
SERIAL NO.

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11. BUDGET DATA:

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12. BUDGET ACTIVITY: RESEARCH.

13. NONE.

14. NONE.

Honors, Awards, and Publications

16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

None

17. HONORS AND AWARDS TO PERSONNEL DURING 1955:

None

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Medical Neurology
BRANCH

3. Neurological Disorder Service
SECTION

4. ________
LOCATION

5. NINDB-6 (C)
SERIAL NO.

6. Histopathological Investigations of Neuromuscular Disorders
PROJECT TITLE

7. G. Milton Shy, M.D.
PRINCIPLE INVESTIGATOR

8. J. Godwin Greenfield, M. D., Ellsworth C. Alvord, M. D., Leonard Berg, M.D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: Two in nature -- 1. To determine histological foundations for neuromuscular diseases 2. To carry on further studies in elucidation of some of the pathological changes noted.

Method employed: Sections of muscle and peripheral nerve are examined following paraffin embedding and frozen sectioning with a variety of techniques to demonstrate anatomical changes in cross striations, nuclei, connective tissue, reticulin, nerve axons and lipids.

Patient material: One hundred and seventy-six patients obtained from the Medical Neurology Branch, NINDB.

Major findings: One hundred and seventy-six muscle biopsies from a variety of neuromuscular disorders including muscular dystrophy, myasthenia gravis, myositis and neuropathies have been received and studied. The first objective has been accomplished in an "Atlas of Pathology of Neuromuscular Disease." It has been completed and will be published by E. & S. Livingstone at Edinburgh.

Conclusions: In most neuromuscular disorders clinical and histological observations complement each other, thus allowing classical examples of neurogenic muscular atrophies, dystrophia myotonica, myasthenia gravis, and other diseases to be relatively easily recognized. In such cases, studied by many investigators over several decades, the areas of disagreement generally concern those of more precise etiology and pathogenesis rather than of observation and interpretation of clinical and microscopic abnormalities.

In many cases, however, there is a discrepancy between the clinical and histological observations. In certain of these, if the histological observations are clear-cut, and if the clinical observations are not unequivocal, one may well accept the histological diagnosis, recognizing that there are exceptions to any clinical rule and that the microscope might well reveal changes which otherwise would not be recognizable. Thus, distal muscular syndromes include not only the usual "neurogenic" muscular atrophies and dystrophia myotonica but also "inflammatory" and "degenerative" forms of "myogenic" disease. Furthermore, among the cases with proximal muscular weakness and wasting there are a few cases of "neurogenic" muscle atrophy, especially amyotrophic lateral sclerosis and "flabby infants", and of dystrophia myotonica.

In certain other cases, however, the discrepancy between the clinical and histological observations is less easily resolved. In our experience this is true of the proximal muscular syndromes in which an attempt is made histologically to distinguish between "inflammatory" and "degenerative" disorders: i.e., between various forms of "muscular dystrophy" and "myositis". We have not been able to reach any satisfactory solution to this difficult problem. At times one wonders whether the muscle biopsy is really helpful, but this pessimistic view cannot long be maintained: one cannot help but feel that further study of more cases will disclose the answers. In this situation we have found that the microscopist preferably should not know the clinical impressions: we have repeatedly seen how remarkably difficult it is to record unbiased observations if the clinical diagnosis is known. If accurate observations can be made, recorded, carefully analyzed and continuously reviewed, our present ignorance and confusion will be replaced by understanding as the result of continued investigations.

Significance to neurological research as can be seen from the results: Many controversial fields are present in the correlation of clinical disease and muscle pathology. This study has clarified the points listed above, but in addition, has raised additional controversies. An original classification of diseases of the lower motor neuron has been offered. An atlas with some seventy colored prints will be available in March to aid other investigators in their studies of these diseases.

Proposed course of the project: The proposed course of this project will reside around the second objective: the elucidations of particular pathological changes associated with neuromuscular disease. In particular, this will reside in the fields of Polarizing Microscopy and Electron Microscopy. This is of particular interest in the proximal myopathies where structural detail may still be present with changes in the biorefractility of the muscle fiber.

R.P.C. 2
Dec. 1955

NINDB-6 (C)-2)
SERIAL NO.

Analysis of NIH Program Activities

Budget Data

10. NINDB (C-2)
SERIAL NO.

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11. Budget Data

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12. BUDGET ACTIVITY: Research

13.

NONE

14.

NONE

Honors, Awards, and Publications

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16. Publications

Atlas of Muscle Pathology. E. & S. Livingstone, Edinburgh, England.

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17. Honors and Awards

NONE

R.P.C. 1
December 1955

Analysis of NIH Program Activities

Project Description

1. Neurology
INSTITUTE

2. Medical Neurology
LABORATORY OR BRANCH

3. Neurological Disorders Service
SECTION

4.
LOCATION

5. NINDB-7 (C)
SERIAL NO.

6. Study of the short-term effect of INH on the course of Multiple Sclerosis.
PROJECT TITLE

7. G. R. Haase, M. D. and M. C. Korengold, M. D.
PRINCIPAL INVESTIGATORS

8. Kenneth R. Magee, M. D. and Leonard Berg, M. D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Project: Study of the short-term effect of INH on the course of Multiple Sclerosis, which were described as dramatic in a recent study. (The Effects of Isoniazid on Patients with Multiple Sclerosis, Kurtzke and Berlin, The Am. Rev. of Tuberculosis, Vol. 70, No. 4, October, 1954.)

Methods Employed: This was a clinical study. Patients who were clearly afflicted with multiple sclerosis were followed as in- and Outpatients. The total patient group was divided into two sub-groups, which were matched as nearly as possible. Employing the "double-blind method", one sub-group received INH while the control group received a placebo. Both groups were re-examined frequently to determine any alterations in the patient's status. The criteria for inclusion in the study included a clear-cut dissemination of lesions within the central nervous system and a dissemination in the onset of various unrelated symptoms in time. Such patients in whom the diagnosis was questionable were excluded from participation in the study.

Patient Material:		No.	Average Stay
Admissions:	Adult males	7	90 days
	Adult females	4	90 days
	Children male	-	-
	Children female	-	-
Outpatient:	Number of patients	70	
	Number of visits	200	

Major Findings: Acute exacerbations were not prevented by the use of INH and beneficial effects of INH in multiple sclerosis were not proved.

Significance to Neurological Research: A major research project is at present underway in the Veterans' Administration based on the work of Kurtzke and Berlin as to the effects of INH in multiple sclerosis. This study was the first controlled double-blind study and does not support the findings of Kurtzke and Berlin.

Proposed course of Project: Terminated.

R.P.C. 2
December 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB-7 (C)
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: RESEARCH

13. NONE.

14. NONE.

Honors, Awards, and Publications

16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

Korengold, M. D., Haase, G. R., Berg, L., and Magee, K. R.
Isonicotinic Acid Hydrazide in Multiple Sclerosis.
J. Neurology, Vol. 5, No. 11, November, 1955.

17. HONORS AND AWARDS TO PERSONNEL DURING 1955:

None

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Medical Neurology
BRANCH

3. Neurological Disorders Service
SECTION

4. -
LOCATION

5. NINDB-8 (C)
SERIAL NO.

6. Recording of Motor End Plate Potentials of Mammalian Muscles
PROJECT TITLE

Specifically in Normal and Myasthenic Man

7. G. Milton Shy, M.D., Choh-Luh Li, M.D., Paul Fatt, M.D.
PRINCIPAL INVESTIGATORS

8. Mr. Jay Wells
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective: To determine if substances are present that compete with or block release of myoneurol humoral substances in myasthenia gravis, or if depolarization exists.

Method employed: Micro-electrode recording from within the single muscle fiber by means of the technique described by Fatt and Katz will be utilized. The lumbricalis muscle will be the one recorded. The ulnar nerve will be stimulated in the forearm and the intramuscular potential recorded through a .5 micron diameter glass pipette led through a cathode follower. The motor end plate potential and the action potential will be recorded by an AC beam of the Dumont Scopė. The resting potential muscle will be recorded on a DC beam.

Patient Material: None to date.

Major Findings: Motor end plate potentials have been successfully recorded from curarized muscle of frog and rat to date, as well as the resting potential.

Significance to neurological research: If the substance causing myasthenia gravis is a curarizing material, then a given end plate potential would demonstrate no spectrum in it's amplitude. If the difficulty is in the release of acetylcholyne then a spectrum should be seen. The presence of a motor end plate potential without the simultaneous firing of the muscle is indicative that one of these mechanisms is in action.

Proposed course of project: A number of patients will be admitted with selective weakness to isolated muscles which will render recording from such muscles easy when nerves supply in such muscles are stimulated at some distance. If isolated motor end plate potentials are found, then various drugs will be given intra-arterially to try to change the electrical recording.

R.P.C. 2
Dec. 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-8 (C)
SERIAL NO.

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11. BUDGET DATA

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12. BUDGET ACTIVITY: Research

13. None

14. None

Honors, Awards, and Publications

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16. PUBLICATIONS FROM THIS PROJECT DURING 1955: None

17. HONORS AND AWARDS TO PERSONNEL DURING 1955: None

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Medical Neurology
LABORATORY OR BRANCH

3. Neurological Disorders Service
SECTION

4. -
LOCATION

5. NINDB-9 (C)
SERIAL NO.

6. Studies in Myoclonus.
PROJECT TITLE

7. Charles E. Wells, M. D.
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objective: To further elucidate the nature of myoclonus, especially in regard to its clinical, electrical, and pathologic aspects; to assess the value of various drugs upon the myoclonus; and especially to establish this as a clear entity separate from other forms of abnormal movements.

Method employed: Patients will be studied by means of electromyography and electroencephalography, in addition to extensive clinical descriptions and evaluations. Movies will be made where possible to correlate clinical and pathologic findings.

Major Findings: Two patients with myoclonus have been studied within the past year by the methods described above correlating electroencephalographic and electromyographic changes with the clinical findings. In one of these patients, complete pathological correlation has also been possible.

Significance to Neurological Research: The subject of myoclonus is marked in the literature by a mass of unclear descriptions and indistinct terminology. It is hoped that a systematic study of the condition will lead to its clear definition as a clinical entity.

Proposed course of Project: It is proposed to study as many patients as possible with this condition during the next year, with the wish that perhaps five patients will be available for study.

R.P.C. 2
Dec. 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-9 (C)
SERIAL NO.

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11. BUDGET DATA

	EST. EXPEND.	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF.	OTHER	TOTAL	PROF.	OTHER	TOTAL	
FY 1956								
FY 1957								

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12. BUDGET ACTIVITY:

RESEARCH	☐	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	TECHNICAL ASSISTANCE	☐

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13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.

None

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE IDENTIFY SUCH PROJECT.

None

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16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

None

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17. HONORS AND AWARDS TO PERSONNEL DURING 1955:

None

R.P.C. 1
December 1955

Analysis of NIH Program Activities

Project Description

1. Neurology
INSTITUTE

2. Medical Neurology
BRANCH

3. Neurological Disorders Service
SECTION

4.
LOCATION

5. NINDB-10 (C)
SERIAL NO.

6. Clinical Studies on Amyotrophic Lateral Sclerosis.
PROJECT TITLE

7. Leonard T. Kurland, M. D. and Kenneth R. Magee, M. D.
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objective: A long term study to evaluate possible metabolic abnormalities in amyotrophic lateral sclerosis and to evaluate various agents as to their therapeutic efficacy in this disease.

Methods Employed: This will be a clinical study. A series of approximately 10 patients with amyotrophic lateral sclerosis will be admitted.

In addition to routine blood and cerebrospinal fluid studies, attempts will be made to determine the blood and cerebrospinal fluid amino acids to seek any abnormality. This will be done by the methods of paper chromatography.

Considering the possibility that amyotrophic lateral sclerosis may be a deficiency disease due to the failure of absorption of some vital food element from the stomach, one or more of the patients will be given repeated blood transfusions and parenteral amino acids and vitamins in an attempt to provide all necessary dietary elements without depending on gastric absorption.

Additional attempts at therapy will be made but their nature will depend on preliminary results of the investigation.

Major Findings: None.

Significance to Neurological Research: Amyotrophic lateral sclerosis is universally fatal. As very little is known concerning its etiology and no treatment exists, attempts to further our knowledge regarding this disease are of the utmost importancy and constitute one of the greatest needs of Neurology.

10. NINDB-10 (C)
SERIAL NO.

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11. BUDGET DATA:

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12. BUDGET ACTIVITY: RESEARCH.

13. NONE.

14. NONE.

Honors, Awards, and Publications

16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

None

17. HONORS AND AWARDS TO PERSONNEL DURING 1955:

None

R.P.C. - 1
December 1955 Analysis of NIH Program Activities

Project Description Sheet

1. N.I.N.D.B.
INSTITUTE

2. Medical Neurology
LABORATORY OR BRANCH

3. Clinical Neurochemistry
SECTION

4.
LOCATION

5. NINDB-11 (C)
SERIAL NO.

6. Glutamine and Glutamic Acid Metabolism in Normal and Epileptogenic Cerebral Cortex
PROJECT TITLE

7. Dr. Donald B. Tower
PRINCIPAL INVESTIGATOR

8. Dr. Maitland Baldwin, Dr. C. Ajmone-Marsan, Dr. Ellsworth Alvord, Dr. W. C. Curtis, Mr. John Phoenix, Mr. Edmund Peters
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(a) Objectives of this project are to study the in vitro metabolism of glutamine and glutamic acid by slices of cerebral cortex from (1) human patients operated for focal epileptogenic cortical lesions and (2) experimental animals.

(b) Methodology: Methods are essentially the same as those in the previous report on this project (1954-NINDB-15 (c)).

(c) Patient material is obtained from NINDB patients admitted to the Surgical Neurology Branch and operated on for excision of focal epileptogenic cortical foci. Since some of these excisions require removal of overlying or adjacent uninvolved cortex, a small number of non-epileptogenic samples is being accumulated.

(d) Major Findings: During calendar year 1955 studies on the defect in metabolism of glutamic acid by epileptogenic cerebral cortex have continued. One sample of human temporal cortex became available in which it was possible to follow glutamic acid metabolism in an epileptogenic focus and in an adjacent area of uninvolved cortex together with electrocorticographic and histological controls for each. Thus, in the same cortical area from a single patient the difference between epileptogenic and non-epileptogenic cortex could be clearly demonstrated:

	Tissue Glutamic Acid		Tissue Glutamine		Tissue Ammonia	
Sample	Level	Change	Level	Change	Level	Change
Non-Epileptogenic						
Initial	7.35		2.2		2.5	
60 min.	10.35	+3.0	3.75	+1.55	3.05	+0.55
Focal-Epileptogenic						
Initial	7.3		2.85		2.15	
60 min.	6.0	-1.3	4.2	+1.35	2.95	+0.8

These results are consistent with numerous other experiments on the respective samples obtained individually from different patients. No differences histologically could be demonstrated between the two samples despite the pronounced electrocorticographic and biochemical differences, confirming the concept of a biochemical lesion.

In 1954 it was shown that among others L-asparagine added to such tissue slices _in vitro_ would correct this and other defects in epileptogenic cortex. These results suggested that L-asparagine could be metabolized by mammalian brain tissue. With the exception of asparaginases, known to be present in serum of herbivors (especially guinea pig) and in kidney and possibly liver of various mammalian species, and the recent finding by Meister that liver enzymes catalyzed transamination reactions with asparagine, no data is available to support the above contention.

C^{14}-labelled asparagine has been obtained and is being utilized to study this possibility further. Considerable difficulty has been encountered in obtaining labelled asparagine. Through the cooperation of the Process Research Department, Merck and Co., a small amount of DL-asparagine-2, 3-C^{14} was synthesized from C^{14}-maleic anhydride. When chromatographically pure material was incubated with slices of normal cat cortex under the usual experimental conditions, metabolism of asparagine could be clearly demonstrated. The results of this experiment suggest that D-asparagine cannot be utilized since about half the total radioactivity remained as asparagine by chromatography. The remainder was distributed, in order of descending activity, in aspartic acid, glutamic acid, glutamine, and possible traces in alanine and γ-aminobutyric acid, as shown by two-dimensional chromatography with radioautographs and actual counts of activity of each amino acid spot by a gas-flow Geiger counter. Since a 4-carbon compound was added and 5- carbon compounds (glutamic acid and glutamine) showed appreciable activity after incubation of slices, metabolism of the asparagine clearly occurred.

Also in 1955 a new convulsant agent, MEG, a glutamic acid derivative, was made available to us by the Medicinal Chemistry department of Merck and Co. This convulsant has been found by them to give an ideal assay method, using mice, for various anti-convulsants, including glutamine and asparagine. It has been found by us that this convulsant will produce severe, immediate seizures in cats. A study of the glutamic acid metabolism of cerebral cortex from such cats showed a most interesting result - a complete disappearance of glutamic acid but maintenance of glutamine during incubation. Thus, we now have two convulsant agents which affect glutamate metabolism in opposite ways: methionine sulfoximine, which inhibits glutamine synthesis, and MEG, which inhibits glutamic acid maintenance.

(e) Significance of this project: Since seizures are a major concern of NINDB as well as a major neurological problem to the population in general, knowledge of the mechanisms underlying them are essential for development of better and more rational therapy. More fundamentally, knowledge of seizure mechanisms will provide many of the factors which are concerned with neuronal function and activity in general and thus be basic to many problems of neurophysiology and neurological diseases. The defect in glutamic acid metabolism in human epileptogenic brain tissue is one of several components of a biochemical lesion of this tissue, which represents the first such lesion of a major neurological disease to be uncovered.

(f) Proposed course of project: Continuation of present studies is underway. It is proposed to apply the studies with C^{14}-labelled asparagine to human epileptogenic and non-epileptogenic material and to the two convulsant preparations cited above. Such studies should assist materially in elucidating the nature of the metabolic reactions taking place.

In addition it is contemplated that a more precise method for quantitative determination of amino acids in such tissue slices can be adopted as a result of methods developed in another project (NINDB-) from this section. By conversion of amino acids in tissue samples to the dinitrophenyl derivatives, separating individual amino acids by column chromatography, eluting the individual acids and reading each fraction colorimetrically, not only will more precise results be obtained but determinations can be extended to aspartic acid, γ-aminobutyric acid, alanine and other amino acids which cannot at present be quantitated. The above procedure will be tried on slices incubated in the standard fashion. If successful, confirmation of data by previous assay methods will be sought and extension of the studies to other amino acids applied.

R.P.C. - 2
December 1955 Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-11 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED	BUDGETED POSITIONS			MAN YEARS			PATIENT
FY 1956	EXPENDITURES	PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	DAYS
		2	2	4	0.3	0.2	0.5	*
FY 1957		2	2	4	0.3	0.2	0.5	*

* Patient material used is derived from patients admitted to other NINDB projects.

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 OR 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

Research and Development Divisions, Merck & Co., Inc.
Research Division, Wallace & Tiernan Co., Inc.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

None.

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-11 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

Tower, D. B. "The Neurochemistry of Seizures" in Progress in Neurobiology: Neurochemistry V.1, Edited by S. R. Korey and J. I. Nurnberger; New York, Paul B. Hoeber, 1955. In Press.

Tower, D. B. "Neurochemical Aspects of Pyridoxine Metabolism and Function," Am. J. Clin. Nutrition. In Press.

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

None.

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. N.I.N.D.B.
INSTITUTE

2. Medical Neurology
LABORATORY OR BRANCH

3. Clinical Neurochemistry
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA

5. NINDB-12 (C)
SERIAL NO.

6. Clinical Evaluation of the Value of Glutamine or Asparagine for the clinical control of Seizures.
PROJECT TITLE

7. Dr. Donald B. Tower
PRINCIPAL INVESTIGATOR

8. Dr. Charles E. Wells, Dr. C. Ajmone-Marsan
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(a) Objectives of this project are to study the effectiveness of two naturally-occurring amino acid amides, L-asparagine and L-glutamine, in controlling seizures in epileptic patients and to observe their effects on epileptiform activity in the electroencephalogram of suitable patients. This project had its inception in the findings on human epileptogenic cortex *in vitro* that significant, chronic defects in metabolism of acetylcholine, glutamic acid and electrolytes occur which can be reversed by addition *in vitro* to such tissue of either glutamine or asparagine, neither of which appear to affect normal *in vitro* metabolism nor to exhibit any effects when administered in large quantities *in vivo* to normal subjects.

(b) Methodology and Patient Material: See 1954 project report (NINDB-   ).

(c) Major Findings: A total of 45 patients have been studied. Of these five represent preliminary patients, 17 have been discontinued for various reasons, and 23 remain active in the project.

All common types of seizures are represented in the above totals. All types appear to respond in similar fashion to amide therapy.

Results to date can be summarized as follows:

	L-asparagine	L-glutamine	Both	Total*
Total on Therapy	36	10	6	40
Male	24	9	6	27
Female	12	1	0	13
5-15 yrs.	17	6	3	20
16-40 yrs.	18	5	3	20
Duration of Oral Therapy				
Over 2 yrs.	2	0	0	2
1-2 yrs.	5	2	0	7
6-12 months	9	3	2	14
3-6 months	11	2	0	13
0-3 months	8	2	0	10
Evaluation (Over 2 mos.)				
Essentially Seizure-free	4	0	0	4(10%)
Significant Seizure Reduction	17	4	1	22(56%)
No Change	7	5	1	13(34%)
Worse	0	0	0	0
EEG Improvement	10	4	0	14(35%)

Discontinuations have been made for the following reasons: No change after 3 or more months: 7; Side reactions:2, Surgery: 1; Uncooperative parents or patient: 7 - total 17.

No toxicity has been encountered for periods exceeding two years. Repeated laboratory examinations have failed to reveal changes in hematological picture, hepatic or renal function or in routine blood chemistries, except for the expected elevation in B.U.N. and N.P.N. A number of cases with various common skin diseases and a few cases with previous history of anticonvulsant drug allergies have been given asparagine without incident.

Unpleasant side reactions have been encountered in only 3 patients (7.5%), consisting of persistent nausea and vomiting. Transient reactions of this nature have occurred in a number of other cases but have not persisted with continuing medication.

In the majority of patients placed on either amide, increased alertness and general well-being has been spontaneously reported regardless of effect on seizure-control. Among the school-age improved group, resumption of or improvement in schooling has been general and home and social situations have been much improved. The older age-group improved patients have been able to broaden their activities, to resume or do better at college, and to seek employment actively. One patient has done such outstanding work in college (straight A average) since starting on amide therapy that he has been recommended for a Fulbright scholarship to continue his studies in languages.

In several instances unintentional omission of amide therapy has resulted in a prompt relapse to previous seizure frequencies with return to control after resumption of amide doses. In one case in particular this was particularly striking - the patient was hospitalized elsewhere for an unrelated condition; his dose of asparagine in chocolate milk was reduced to one-fifth through a misunderstanding and without the patient's knowledge; daily major and minor seizures ensued whereas before and after this episode on full dosage the patient has remained seizure-free.

3 patients have received DL-asparagine for periods up to several months. Results have been equivocal. 3 patients have received supplemental pyridoxine (Vitamin B_6) orally without effect on seizure frequency. Administration of α-ketoglutarate was tried in one patient but could not be tolerated because of tase and gastric irritation. One patient not otherwise included in this project received L-glutamine (parenteral preparation) intrathecally without untoward reaction.

In the course of studies on this group of patients several subsidiary observations have been possible. One patient has been studied because of high serum CO_2 content and found to be spontaneously hypoventilating. Diamox, a carbonic anhydrase inhibitor, had no effect on this patient's seizure-frequency despite an adequate biochemical response to the drug. In several cases where no change in seizure frequency was obtained with amide **therapy** and where previous anticonvulsant medication had been ineffective, relatively massive doses of Tridione proved very effective in eliminating seizures. In one case with a behavior disorder Reserpine is under trial in conjunction with asparagine. Good seizure control had been obtained with the latter and addition of Reserpine did not affect the control and appears to be controlling behavior.

(d) Significance of this project would seem to be self-evident. It represents a new type of compound which has definite anticonvulsant properties, but which differs from all other anticonvulsants not only in its chemistry but in its lack of toxicity and lack of sedative or hypnotic action. It represents development of therapy based on a demonstrated biochemical lesion in human epileptogenic brain tissue. The number of problem cases referred to NINDB or contained in inquiries from neurologists and physicians in this country and abroad indicate that better, more effective therapy for seizures is in demand. With over a million and a half seizure patients in this country alone, it is a major health and economic concern. In addition this project is representative of the type of research for which the clinical investigation phases of NIH were created in that it has taken laboratory findings, applied them to patient material at the Clinical Center in a detailed manner seldom possible elsewhere, developed agents of considerable initial cost to the point where cost is being lowered to more reasonable ranges, and promoted trials elsewhere (as noted below).

(e) Proposed Course of the project is to continue studies now underway. It is not planned at present to add further patients to the present group except as special occasions may arise. The possibility of obtaining an enterically-coated form of α-ketoglutarate is to be explored since it would be of interest to try this compound clinically because it is the immediate precursor of glutamic acid and might prove as effective as asparagine or glutamine. It is already produced synthetically and would ultimately be quite inexpensive if shown to be effective.

Much of the coming year will be devoted to studies of metabolism of asparagine and glutamine in these patients by methods developed in another project from this Section (NINDB-). These studies are designed to try to correlate dose with clinical response and to determine whether lack of response by some patients may be due to faulty absorption, too rapid elimination or the like.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-12 (c)
SERIAL NO.

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11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	BUDGETED POSITIONS OTHER	BUDGETED POSITIONS TOTAL	MAN YEARS PROF	MAN YEARS OTHER	MAN YEARS TOTAL	PATIENT DAYS
FY 1956		2	2	4	0.8	0.4	1.2	2133*
FY 1957		2	2	4	0.8	0.4	1.2	1000 est

* Actual total for calendar year 1955.

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12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S) (ITEM 1).

(a) Extra-mural grants, coordinated by Section of Clinical Neurochemistry, for assessment of L-asparagine in seizure therapy on approximate 100 patients to:

Harvard Medical School (Children's Medical Center)
University of North Caroline Medical School
University of Buffalo Medical School
University of Maryland Medical School
University of Virginia Medical School

(b) Cooperative studies with Section of Clinical Neurochemistry for individual cases by:

Dr. William Caveness-College of Physicians & Surgeons, N.Y.
Dr. Denis Williams - National Hospital, Queens Square, London, England
Dr. Irwin Levy - Washington University Medical School, St. Louis, Mo.
Dr. Hudson Hoagland - Worcester Foundation, Worcester, Mass.
Dr. Louis Goodman - University of Utah Medical School
Dr. Fred Stamps - University of Chicago Medical School

(c) Research and Development Divisions, Merck & Co., Inc.

R.P.C. - 2a
December 1955

NINDB- 12 (C)
SERIAL NO.

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None.

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-12 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

Tower, D.B. "The Neurochemistry of Seizures" in Progress in Neurobiology: Neurochemistry V. 1, Edited by S. R. Korey and J. I. Nurnberger; New York, Paul B. Hoeber, 1955, In Press.

Tower, D. B. "Neurochemical Aspects of Pyridoxine Metabolism and Function," Am. J. Clin. Nutrition. In Press.

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

None.

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Medical Neurology
LABORATORY OR BRANCH

3. Clinical Neurochemistry
SECTION

4. ______________________________
LOCATION (OTHER THAN BETHESDA)

5. NINDB-13(C
SERIAL NO.

6. Metabolism of Glutamic and Aspartic Acid Amides in vivo
PROJECT TITLE

7. Dr. William C. Curtis and Dr. Donald B. Tower
PRINCIPAL INVESTIGATORS

8. Dr. Charles B. Wells and Mr. John Phoenix
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

(a) OBJECTIVES of this project are to develop suitable clinical methods for simultaneous quantitative determination of glutamic acid, aspartic acid, glutamine and asparagine in body fluids (blood, cerebrospinal fluid, urine) in order to follow the metabolic fate of ingested doses of glutamine and asparagine or both in seizure patients on such therapy and to correlate such findings with oral dosage and clinical response.

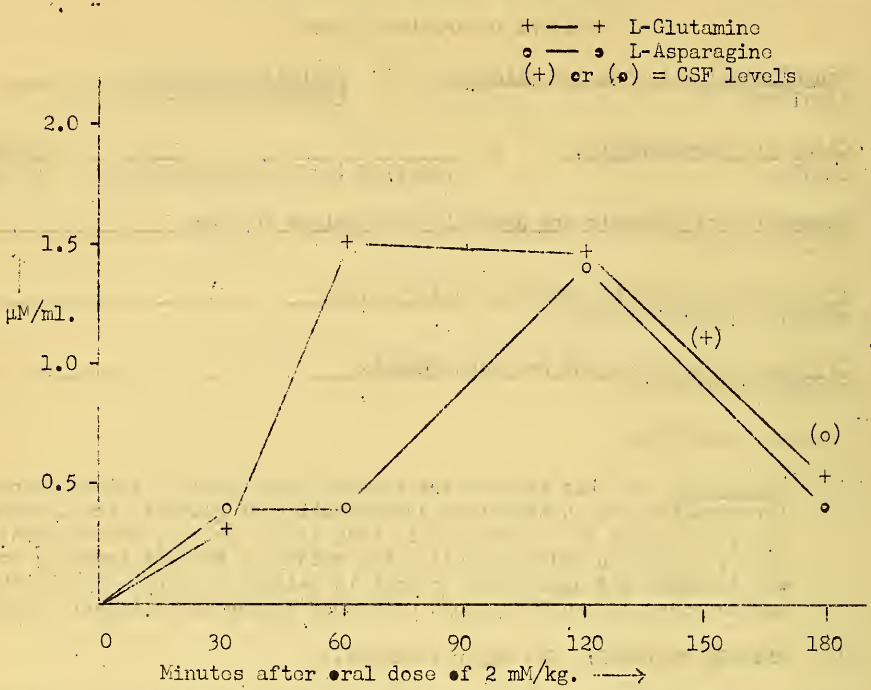
(b) METHODS EMPLOYED: See Major Findings.

(c) PATIENT MATERIAL: will be derived from the patients being studied in the clinical study assessing the anticonvulsant effectiveness of glutamine and asparagine (Serial #   ). Other NINDB patients not on such therapy will be used for acute studies.

(d) MAJOR FINDINGS: The majority of calendar 1955 has been devoted to working out details of the method for determination of glutamic and aspartic acids and their amides in body fluids.

Preliminary runs on plasma and spinal fluid samples for asparagine only have given satisfactory results. After an oral dose of 2 mM/Kg. of L-asparagine, the plasma level rises to a maximum of 0.7-1.5 μM./ml. (10-20 mg. %) at 90-120 minutes after ingestion, and drops to control levels by about 180-210 minutes. Single spinal fluid samples at 180 minutes have shown asparagine levels of about 0.7 μM/ml. (10 mg. %), which are generally higher than plasma levels at this time. Since there is virtually no asparagine normally detectable in plasma or spinal fluid these results represent essentially absolute increases. The rise obtained and the shape of the curve are quite similar to those obtained for glutamine under the same conditions (See 1954 report NINDB-17(C)). Similar results for asparagine have been obtained by Van Buskirk, using a different method (Personal communication). Representative curves for glutamine and for asparagine are shown here:

AMIDE PLASMA "TOLERANCE" CURVES



Information obtained from determinations of the amide concentrations alone did not seem to offer as much value from a metabolic standpoint as determination of all possible compounds concerned. Therefore collection of patient data has been deferred pending modification of the method to permit simultaneous determination of glutamic acid, aspartic acid, glutamine and asparagine in the sample. This objective has been largely achieved. The method is as follows:

(1) Sample: 1-3 ml. of blood plasma or spinal fluid are used. Blood is collected in heparinized tubes.

(2) Deproteinization: The usual clinical methods of deproteinization were found to be unsatisfactory. Trichloracetic acid could not be used because of its interference with subsequent steps in the procedure. Tungstate precipitation reduced recoveries to too great a degree. It was found possible to deproteinize the samples by passing the sample through a small column of Dowex-50 chromatographic cationic exchange resin. The proteins pass through while the amino acids are held on the column. The amino acids are then eluted with 0.8 N HCl in 55% ethanol and the eluant evaporated to dryness, using a Roto-Vac evaporator with mild vacuum and heating not over 55° C.

(3) Conversion of Amino Acids to Dinitrophenyl Derivatives: The amino acid mixture is dissolved in a small volume of 2.5 N HCl and placed in an autotitrator unit in a water bath at 40°C. The solution is brought to pH 9.0 with alkali (usually NaOH). Excess fluorodinitrobenzene is added and the reaction continued for 80 minutes at pH 9.0 and 40°C with mechanical stirring. This procedure converts all amino acids and amines to their yellow-colored dinitrophenyl derivatives. Excess reagent is removed by extraction of the alkaline solution with ether.

(4) Chromatographic Separation of Amino Acids: The aqueous solution is acidified with 1 ml. of 5N HCl and re-extracted with ether. The acid and neutral amino acids, including glutamic and aspartic acids, asparagine and glutamine, now go into the ether phase, leaving the basic amino acids in the aqueous phase. The ether phase is evaporated to dryness, using the Roto-Vac evaporator, and the residue taken up in 10 ml. of a 50-50 ether-chloroform mixture. This solution is then applied to a lightly packed Celite (diatomaceous silica) column, 40 cm. in length and 1 cm. in diameter buffered at pH 4.0 with phosphate buffer. 50-50 ether chloroform is then run through the column. Six amino acids are held on the column. In their order from top to bottom they are: asparagine, glutamine, aspartic acid, serine, threonine and glutamic acid. All other amino acids in the acid fraction applied to the column are eluted in the first 10 ml. from the column.

(5) Elution and Determination of Amino Acids: The six amino acids on the column are then eluted successively. Glutamic acid followed in order by threonine, serine and aspartic acid are eluted with 50-50 ether-chloroform and collected in individual fractions. Glutamine and asparagine are then successively eluted with 95-5 ether-chloroform. The six eluant fractions are evaporated to dryness and the residue taken up in 1% $NaHCO_3$ to a standard volume. The yellow-colored solutions are read at 360 mμ in a Beckman spectrophotometer against appropriate dinitrophenyl derivatives of each amino acid. The range of concentration which can be determined is 0.005-0.08 μM (about 1-10 μg.) in most cases.

The above procedure is to our knowledge the first which permits direct determination of glutamine, since all previous methods of this type involve hydrolysis of the glutamine to glutamic acid before determination. The above procedure is also to our knowledge the first to permit simultaneous determination of the four very closely related amino acid compounds, glutamic acid, glutamine, aspartic acid, and asparagine by a relatively simple, quantitative chemical method. Previous methods have generally involved the use of specific bacterial enzymes and manometric techniques, which are much more cumbersome and time consuming and less sensitive. The present method is also rather time consuming when all four compounds are determined, but can be speeded up considerably for determination of asparagine or glutamine alone.

The present method has a much wider application than that being used here. All amino acids in the original biological sample are quantitatively converted to their dinitrophenyl derivatives. Three fractions are obtained in the procedure subsequently outlined: I. - basic amino acids, such as lysine, separated by the extraction with ether; II. - all acid and neutral amino acids except glutamic acid, aspartic acid, glutamine, asparagine, serine and threonine, separated by passage through the column without adsorption; and III. - the six amino acids held on the column. Fractions I and II could be separated by appropriate column and pH conditions into their individual components in a manner analogous to that used here for fraction III.

Many problems have been encountered in the development of this method which will not be detailed here. Because of the potential value of this method for many problems it was deemed essential to have every stage in the procedure thoroughly checked, reproducible and standardized for ready use by others. Therefore most of the time during calendar 1955 has been devoted to this phase of the project.

Preliminary runs by the above method of plasma samples from patients receiving oral asparagine therapy have been carried out. No signficant changes in plasma glutamine or glutamic acid levels occur during the rise and fall of asparagine level (see graph above). Aspartic acid rises to a peak value about 25% of the asparagine peak value some 60 minutes after the asparagine peak, indicating some deamidation of asparagine during that period but not sufficient to account for the total asparagine determined.

(e) SIGNIFICANCE TO THE PROGRAM OF THE INSTITUTE: Significance of this project is in the interpretation of results being obtained in clinical therapy with glutamine and asparagine. With the use of any new compound for therapy it is important to be able to determine it in body fluids, to know the course of its metabolism and to be able to correlate dose, body level and clinical effect. With the quantities of amides being administered this becomes even more important.

(f) PROPOSED COURSE OF THE PROJECT: The method developed is to be rechecked against the available microbiological methods for glutamic acid, glutamine and asparagine and then published.

Patient samples (plasma and spinal fluid) will be run serially and in sufficient numbers to obtain the following data: (1) type or types of plasma and spinal fluid curves obtained from control patients given single oral doses of either glutamine or asparagine or both; (2) types of curves shown by seizure patients on daily doses of either or both compounds; (3) comparison of such data with clinical responses of patients; (4) determination of metabolic course of the compounds as reflected by plasma and spinal fluid changes.

Urinary studies will be added to the above as soon as methods have been modified for this purpose. Semi-quantitation is already being obtained, using paper-chromatography of the dinitrophenyl derivatives of amino acids in the urine, but adaptation of the column method is being tried. Urine presents a difficult problem compared to other body fluids so that considerable work will be entailed in this phase.

Finally adaptation of the method for tissue determination will shortly be instituted. Methods currently available and in use in this laboratory do not permit simultaneous quantitation of all amino acids present in the size of sample available, and for some of these amino acids no satisfactory quantitative methods are available. Such a method will be most useful in this project and in another project of this laboratory (NINDB-) concerned with brain amino acid metabolism.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB- 13 (C)
SERIAL NO.

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11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1956		3	2	5	0.5	0.5	1.0	*
FY 1957		3	2	5	0.5	0.5	1.0	*

* Patient material used is derived from patients admitted for other NINDB projects

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12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 OR 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

National Cancer Institute - Dr. Alton Meister

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14. IF THIS PROJECT, RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH).

None

R.P.C. 3
December 1955

NINDB-13 (C)
SERIAL NO.

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

None

R.P.C. - 1
December 1955 Analysis of NIH Program Activities

Project Description Sheet

1. N.I.N.D.B.
INSTITUTE

2. Medical Neurology
LABORATORY OR BRANCH

3. Clinical Neurochemistry
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NINDB-14 (C)
SERIAL NO.

6. Electrolyte Metabolism and Energy Metabolism in Normal and Epileptogenic Cerebral Cortex
PROJECT TITLE

7. Dr. Donald B. Tower
PRINCIPAL INVESTIGATOR

8. Dr. Maitland Baldwin, Dr. C. Ajmone-Marsan, Dr. Ellsworth Alvord, Mr. Edmund Peters and Dr. Beni Horvath.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(a) Objectives of this project are to study the *in vitro* metabolism of electrolytes, sodium and potassium, and of energy-producing cycles and compounds by slices of cerebral cortex from (1) human patients operated on for focal epileptogenic cortical lesions and (2) experimental animals.

(b) Methodology and Patient Material: See 1954 report (NINDB-18(C)).

(c) Major Findings: Further studies in this project have been delayed pending development of suitable methods for obtaining data desired. Two problems are involved. The first concerns valid determination of tissue electrolyte concentration which, to be meaningful, must be expressed per unit of intracellular water. The latter requires measurement of the intracellular space for which no satisfactory method is currently available. We have learned that Engstrom in Sweden has developed but not yet reported an X-ray diffraction or absorption method which will accurately determine extra- and intracellular spaces in fresh tissue sections. We are therefore awaiting word on this possibility before resorting to the less reliable methods now available.

The second problem concerns the energy metabolism aspect of this project. The studies of Meister and co-workers have demonstrated that in purified enzyme systems, the synthesis of glutamine, which requires high-energy phosphate as ATP, is reversible (Ref. J. Biol. Chem. 209: 265, 1954). In this system, starting with glutamine, ATP is formed from ADP as glutamine is converted to glutamic acid. These experiments provide a more detailed concept of the situation which may exist in epileptogenic brain tissue. On incubation defects occur in metabolic systems which are energy-dependent. At the same time glutamic acid is metabolized by the tissue, substantially reducing the level of this important intermediate. Correction of all defects occurs on addition of glutamine or asparagine. If Meister's results are applicable even to a limited degree, the addition of one or other amide could simultaneously replace metabolized glutamic (or aspartic) acid and provide extra ATP for cellular metabolism.

Two principal studies must be made in order to study the above possibilities. First the manner in which added glutamine or asparagine are metabolized by normal and by epileptogenic brain. Carbon-14 labelled amides as tracers for the addition can be expected to provide much of this information. Preliminary experiments with asparagine have already been carried out (see project NINDB-). However, in addition to amino acids, for which suitable chromatographic methods are available, the α-keto acid derivatives must also be examined since these provide the metabolic link between amino acids. Paper chromatography of the keto compounds has not been well worked out. During calendar 1955 much effort has gone into preparing authentic standard dinitrophenylhydrazones of all anticipate keto compounds and into determining suitable solvents for chromatography. When the studies are completed, it will be possible to trace metabolism, with the radioactive tracer, through the ketoacid compounds, as well as determining the amounts of such compounds by extraction of the chromatographically isolated spots.

The second study involves direct determination of ATP, ADP and Creatine phosphate levels in normal and epileptogenic brain tissue with or without added glutamine or asparagine. Specific muscle enzymes for each of these high-energy phosphate compounds have been developed in this laboratory for use in these studies.

(d) Significance of this project is self-evident since it brings into these studies on epileptogenic cortex two factors, electrolytes and energy supplies, which are accepted as essential to neuronal activity and function, providing much evidence for the mechanism by which seizures can occur. If these findings can be clarified and extended, many of the missing links in the chain of circumstances underlining the seizure and concerned with neuronal activity in general can be set in place. This will represent a contribution not only to the problem of seizures but to neurophysiological mechanisms in general.

(e) Proposed course: See under Major Findings.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-14 (C)
SERIAL NO.

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11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY '56		2	2	4	0.2	0.3	0.5	*
FY '57		2	2	4	0.2	0.3	0.5	

* Patient material is derived from patients admitted for other NINDB projects.

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12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 OR 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) ITEM 1

None

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

None

R.P.C. - 3
December 1955

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NINDB-14 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

Tower, D. B. "The Neurochemistry of Seizures" Progress in Neurobiology: Neurochemistry Vol. 1, edited by S. R. Korey and J. I. Nurnberger; New York, Paul B. Hoeber, 1955. In Press

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

None.

R.P.C. - 1
December 1955

Analysis of NIH Program Activities
Project Description Sheet

1. N.I.N.D.B.
INSTITUTE

2. Medical Neurology
LABORATORY OR BRANCH

3. Clinical Neurochemistry
SECTION

4. LOCATION(IF OTHER THAN BETHESDA)

5. NINDB-15(C)
SERIAL NO.

6. Electrophoretic Studies of Human Cerebrospinal Fluid Proteins in Demyelinizing Diseases
PROJECT TITLE

7. Dr. William C. Curtis and Dr. Donald B. Tower
PRINCIPAL INVESTIGATORS

8. Dr. Charles E. Wells, Mr. John Phoenix and Mr. Edmund Peters
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(a) Objectives of this project are to study the abnormalities in the protein fractions of cerebrospinal fluids from patients with multiple sclerosis in order to determine the significance of such abnormalities both diagnostically and prognostically in the clinical course of the disease.

(b) Methodology: Cerebrospinal fluid samples are obtained from NINDB ward or outpatients by lumbar puncture or during pneumoencephalography. Aliquots of these samples are examined for routine constituents.

Total protein content of the fluid samples is determined by refractometry or ultra-violet absorption or both. Each method is calibrated by Kjeldahl and gravimetric runs on spinal fluid samples.

Routine electrophoresis of all spinal fluid protein fractions is run by paper-strip electrophoresis or by micro-interferometric electrophoresis or both, as detailed previously (see 1954 NINDB-20 (C)). Where appropriate serum samples from the same patient are run simultaneously.

Fractionation of spinal fluid protein for individual study will be attempted in several ways: by electro-convection isolation, by counter-current distribution (if this can be adapted), and by column electrophoresis-chromatography. Separated fractions, especially gamma-globulins, will be studied by micro-interferometric electrophoresis for homogeneity and mobility. The separated fractions will also be studied by paper-strip electrophoresis with staining for associated lipid and carbohydrate by Sudan Black and Feulgen reagents respectively. Semi-quantitation of paper runs is carried out with a Spinco analytrol scanner.

(c) Patient material: No patients have as yet been specifically admitted to this project. Patient material so far has been obtained from other NINDB project patients. As studies progress suitable patients with multiple sclerosis will be selected for serial study of their fluid patterns to permit correlation with the clinical state and progress of the disease.

(d) Major findings: In calendar 1955 paper-strip studies begun in 1954 were continued. As a result of the study of some 60 patients, half of whom had multiple sclerosis, confirmation of the previous findings of Kabat et al (Ann. N.Y. Acad. Sci. 58: 613 (1954)) have been obtained. The percentage of fluids from cases of multiple sclerosis with elevated gamma globulins in both cases was about 65%. In both series early cases or cases with few and infrequent attacks the percentage of positive fluids was much lower. Serial sampling of given patients has tended to show persistance of elevation where such elevation was found initially. However, in both series elevated gamma globulin has been found in spinal fluids from cases with other neurological diseases, especially the hereditary cerebellar ataxias. Elevations are also known to occur in neurosyphilis and certain types of meningitis.

The results of this type of study clearly indicate that elevation of spinal fluid gamma globulin occurs in most patients with multiple sclerosis. However, this observation appears to be of little value diagnostically, since the elevation precedes clinical symptoms in too few cases to be of clinical use. It is also of little value prognostically since clear-cut variations in suitable selected patients have not been observed. And it is of little value etiologically since a number of apparently unrelated conditions show similar elevations and since the source of the gamma globulin is not indicated by such studies.

Thus, this approach appeared to offer little value in its continuation. After considerable effort it has still not been possible to demonstrate lipid or carbohydrate in association with spinal fluid protein fractions, although such are readily detected for serum by the same methods. It seemed, therefore, that a more basic approach to this problem is needed and the studies have been halted pending development of this phase (see below).

(e) Significance of this project is self-evident, since it represents a detailed study into an established chemical abnormality in a disease, multiple sclerosis, which is a major problem not only from a public health standpoint but from a diagnostic, prognostic and therapeutic standpoint. Nothing is known about its course or the mechanisms underlying its cause. With this first clue of biochemical abnormality a step in the direction of covering these many problems can be made by such a detailed and long-term approach.

(f) Proposed course: From serum and immunological studies it is now known that gamma-globulin is not a single entity but consists of a mixture of at least four to six types. The usual methods for demonstrating and isolating these types require too much protein to be applicable to spinal fluid studies. However, by newer physico-chemical techniques it seems possible that isolation of gamma-globulins from spinal fluid can be achieved in sufficient amounts to permit characterization by micro techniques.

Therefore, it is proposed that the following course of investigation be instituted during the coming year:

(1) Perfection of methods for isolation of the gamma-globulin fraction from spinal fluid and serum, probably by electro-convection and/or column electrophoresis methods,

(2) Comparison of (a) spinal fluid gamma-globulins with serum gamma-globulins from the same patient and (b) spinal fluid gamma-globulins from patients with and without elevations (ie. multiple slerotics vs. non-multiple sclerotics), by various physico-chemical methods, primarily micro-interferometric electrophoresis, ultra-violet absorption, and if possible counter-current distribution. This phase is designed to determine whether serum and spinal fluid gamma-globulins are identical and whether the rise in gamma globulin in spinal fluids of multiple sclerotics is due to the same or different gamma globulin compared to that present in control patients.

(3) With concentrated, isolated specimens of gamma-globulins paper-strip electrophoresis will be used to determine whether, with greater concentrations than those possible in usual spinal fluid runs, lipid and/or carbohydrate associated groups can be demonstrated.

It is possible that immunological methods may have to be resorted to to demonstrate differences between gamma-globulins if the above methods are not sensitive enough.

The above procedures will be applicable to other protein fractions as well. In the course of these studies isolation of alpha- and beta-globulins will also be undertaken for characterization by the same procedures.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-15 (C)
SERIAL NO.

11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1956		3	2	5	0.3	0.2	0.5	*
FY 1957		3	2	5	0.3	0.2	0.5	

* Patient material used is derived from patients admitted to other NINDB projects.

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 OR 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM I)

National Institute of Arthritis & Metabolic Diseases-Dr. Saroff.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS); IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH).

None

R.P.C. - 3
December 1955

Analysis of NIH Program Activities
Honors, Awards, and Publications Sheet

15. NINDB-15 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

None

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

None

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. N.I.N.D.B.
INSTITUTE

2. Medical Neurology
LABORATORY OR BRANCH

3. Clinical Neurochemistry
SECTION

4.
LOCATION

5. NINDB- 16 (C)
SERIAL NO.

6. Pentosuria in Neuromuscular Disease
PROJECT TITLE

7. Dr. Donald B. Tower
PRINCIPAL INVESTIGATOR

8. Dr. G. Milton Shy, Mr. Edmund Peters, Mr. Milton Pogorelskin
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(a) Objectives of this project are to assess the importance, if any of pentosuria in patients with primary muscle disease and to identify the quantity and type of pentoses being excreted.

(b) Methodology: See previous report (1954-NINDB-19(C)

(c) Patient material is obtained from NINDB ward patients. Neuromuscular disease patients are admitted to Medical Neurology for other studies and urine specimens provided for this project. Other patients with no muscle disease serve as controls and are derived from other NINDB ward patients with eye diseases, multiple sclerosis, seizures and the like.

(d) Major Findings: This project was completed during the first half of calendar 1955 and is to be published shortly. The results of the project can be summarized as follows:

(1) The quantitative excretion of free aldopentoses in 230 twenty-four hour urine specimens from 55 patients with and without muscle disease were studied by the para-bromaniline method. All patients were on fruit-free diets during study.

(2) The mean excretions of total free aldopentoses per 24 hours per kg. body weight were: (a) by patients with no muscle disese 3.6 μM for adults and 5.5 μM for children (under 15 years of age); and (b) by patients with myopathies 6.6 μM for adults and 9.6 μM for children. Differences between means of the two groups of adults or of children were statistically significant in both cases.

(3) Identities of the pentoses excreted were established by 29 two-dimensional paper chromatograms of 24-hour urine specimens from 18 patients. Eight carbohydrate compounds were identified. The majority of specimens contained glucose, xylose, arabinose and ribose. A few exhibited spots identified as lactose, galactose, desoxyribose and a uronide (?glucuronic acid). No ketoses were detected in regular or concentrated specimens with the possible exception of fructose. No differences in the patterns of carbohydrates excreted were apparent between the group with and that without muscle disease.

(4) Semi-quantitation of aldopentoses excreted was carried out by the spot area method on one-dimensional chromatograms of 14 24-hour urine specimens from 12 patients. Arabinose predominated in specimens from the group with no muscle disease, whereas ribose appeared to be significantly higher in specimens from the group with muscle diseases. Xylose appeared to be about the same in both groups.

(5) The findings suggest that patients with muscular dystrophy, myotonia dystrophica, myasthenia gravis and muscular atrophy (?cause) excrete significantly higher amounts of free aldopentoses in 24 hours, largely accounted for as ribose, than patients with diseases such as multiple sclerosis, spinal cord disease, cerebral seizures and uveitis.

(6) No correlation of these findings with clinical status of the muscle disease patients (based upon duration of disease, rate of progression, degree of muscle involvement and disability, histopathology, and electromyography) could be established.

(7) Good correlation of μM pentoses excreted 24/hrs/kg. body weight with residual functional muscle mass (as measured by potassium exchanged per kg. body weight (Ke/Kg) obtained in a separate study (see 1954-NINDB-3(C)) was demonstrated for 22 adult patients for whom both sets of data were available. The coefficient of correlation was statistically highly significant. This finding suggests that, as residual functional muscle mass is reduced, the excretion of pentoses, mostly as ribose, increases in the urine.

(8) Thus, the results obtained in this project relate pentosuria in muscle disease to the result of muscle wasting, probably related to the breakdown of nucleoproteins and nucleic acids and the inability of the muscle to salvage the ribose so liberated.

(e) Significance of this project is primarily to establish definitively whether or not there is an abnormal degree or type of pentosuria in patients with primary muscle disease. Clues to the possible causes or mechanisms underlying muscular dystrophy in particular are virtually non-existent. It is important, therefore, to reach a conclusion about pentosuria, particularly since the literature is now confused and incomplete on this point. If there is a significant abnormality here, it will be of great importance and warrant extension to studies of blood and muscle. On the other hand definite negative evidence will be of service in directing efforts elsewhere and clearing confusion in the literature. Since neuromuscular diseases are one of the principal programs of NINDB, this project is important as one phase of that study.

(f) Proposed Course: This project is completed. No further studies are contemplated at this time.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-16 (C)
SERIAL NO.

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11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1956	None	0	0	0	0	0	0	0
FY 1957	None	0	0	0	0	0	0	0

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12. BUDGET ACTIVITY

RESEARCH ☒ ADMINISTRATION ☐

REVIEW AND APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 OR 1957; IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

None

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH).

None

R.P.C. - 3
December 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheets

15. NINDB-16 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

Tower, D. B., Peters, E. L. and Pogorelskin, M.A., "Nature and Significance of Pentosuria in Neuromuscular Diseases" Neurology 6: In Press (Jan and Feb, 1956).

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

Master of Science Degree, Georgetown University for a portion of this study - M. A. Pogorelskin.

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Medical Neurology
LABORATORY OR BRANCH

3. Clinical Neurochemistry
SECTION

4. ______________________________
LOCATION(OTHER THAN BETHESDA)

5. NINDB- 17 (C)
SERIAL NO.

6. Comparative Biochemistry of Smooth Muscle & Striated Muscle Actomyosin
PROJECT TITLE

7. Beni Horvath, M.D.
PRINCIPAL INVESTIGATOR

8. Mr. Joseph Proctor
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

(a) Objectives: To characterize the uterine actomyosin in physico-chemical terms, preliminary to a study of actomyosin synthesis in the uterine muscle.

(b) Methods Employed: Myosin and actin will be prepared from rabbit uterine muscle and striated muscle. Yield will be compared at different stages of development of the uterus. The myosin and actin so obtained will be characterized by viscosity, electrophoretic mobility, sedimentation constant etc. as well as by its reaction with ATP.

(c) Major Findings: For the purpose of comparison between the two kinds of muscle an extraction procedure had to be established and standardized giving maximal yield for both type of muscles. The method of Dr. Albert Szent-Gyorgyi, originally devised for extraction of heart muscle, was found to give excellent yields of actomyosin from small samples of skeletal muscle also. This method has the added advantage over the method of Dr. Csapo employed earlier, that the extraction of the homogenized muscle takes only a few minutes rather than overnight. The new method uses Potassium Iodide instead of Potassium Chloride, in an alkaline solution.

(d) Significance to the Program of the Institute: It is felt that studies of formation of myosin and actin may have a relationship to location of disease in muscular dystrophy. Quantitative extraction procedures are also essential for the study of proteins in Neuromuscular Disease.

(e) Proposed Course of Project: Adaptation of the above extraction procedure to the uterine muscles of rabbits, and isolation of actin and myosin from the actomyosin obtained by the method of A.G. Szent Gyorgyi. As the ovarian hormones estrogen and progesterone have a marked effect on the development of the uterus, the effect of these hormones will be studied on the time course of the protein synthesis in the uterine muscle, using the quantity of myosin and actin as an indicator.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-17 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1956		1	1	2	0.4	0.2	0.6	0
FY 1957		1	1	2	0.4	0.2	0.6	0

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEMI)

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH).

None

R.P.C. - 3
December 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB- 17 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

None

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

None

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
2. Medical Neurology
3. Clinical Neurochemistry
SECTION
4.
LOCATION(IF OTHER THAN BETHESDA)
5. NINDB- 18 (C)
SERIAL NO.

6. Alterations of Actomyosin Tensile Strength and Muscle Proteins in Neuromuscular Disease
PROJECT TITLE

7. Dr. Beni Horvath
PRINCIPAL INVESTIGATOR

8. Dr. G. Milton Shy and Dr. William C. Curtis
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

(a) Objective: To determine alterations in tensile strength of Actomyosin threads from biopsy material of patients with neuromuscular disease. To estimate the quantity of Actomyosin in diseased muscles and to characterize in physicochemical terms the proteins of diseases muscles as compared to normals.

(b) Methods: Muscle fibers obtained from patients afflicated with neuromuscular diseases were collected and preserved in glycerol at low temperature for future analysis. The tension developed by these fibers was measured in a specially built apparatus. The tension was studied as a function of the Potassium, Magnesium and ATP concentration of the medium. Samples of normal muscle were compared with samples of myotonic muscles and with samples of muscles suffering from muscular dystrophy and with muscle samples afflicted with dystrophia myotonica.

Other samples also obtained on biopsy were collected and stored in the frozen state. These samples were extracted by the method of Dr. Szent Gyorgyi originally developed for the heart muscle employing an alkaline solution of Potassium Iodide. The actomyosin so prepared was studied in the form of threads. These threads contract in a suitable environment on the addition of ATP. Again the effect of the above variables was studied under identical conditions on the actomyosin prepared from muscles suffering from the above diseases and compared to normal actomyosin.

(c) Patient Material: Muscle sample obtained from patients afflicted with neuromuscular diseases, under nerve block anesthesia.

(d) Major Findings: On the glycerinated fibers it was observed that for normal muscles there is only a narrow range of ATP concentrations where the fibers develop maximal tension. On myotonic fibers and on fibers from muscles with myotonic dystrophy this range appears to be appreciably wider. Muscular Dystrophy fibers now being studied seem to resemble the myotonic ones more than the normals in the early stage of the disease. The effect of the other variables is less pronounced.

The same widening of the range of the optimal ATP concentration was also observed in the shortening experiments carried out on the threads prepared from actomyosin of the myotonic muscles.

(e) Significance: No change.from NINDB -22(C) 1954.

(f) Proposed Course: Experiments along both lines will be extended to include other diseased states. Since it appears that myotonia may involve some alteration of the actomyosin molecule it seems to be desirable to characterize myosin and actin prepared from myotonic muscles by physico-chemical methods.

R.P.C. - 1
December 1955

NINDB- 18 (C)
SERIAL NO.

10. NINDB-
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1956		2	1	3	0.6	0.7	1.3	
FY 1957		2	1	3	0.6	0.7	1.3	

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 OR 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S).

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None.

R.P.C. - 3
December 1955

Analysis of NIH Program Activities

Honors, Awards and Publications Sheet

15. NINDB- 18 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

None.

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

None.

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. N.I.N.D.B.
INSTITUTE

2 Medical Neurology
LABORATORY OR BRANCH

3. Clinical Neurochemistry
SECTION

4.
LOCATION

5. NINDB-19(C)
SERIAL NO.

6. The Nature and Characterization of Oxyproteic Acids, Pyrogens and Similar Molecules
PROJECT TITLE

7. Dr. William C. Curtis
PRINCIPAL INVESTIGATOR

8. Dr. Donald B. Tower, Mr. John Phoenix, Dr. G. M. Shy & Dr. W. Windle
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

(a) Objectives of this project are to develop suitable physicochemical methods for the isolation and characterization of oxyproteic acids, pyrogens and similar molecules. The chemical and physical natures of these compounds are poorly understood and their significance and mechanisms of action remain obscure.

(b) Methodology: Isolation and purification of oxyproteic acids from urine and of the pyrogen, Piromen, will be carried out by ion exchange, column chromatography, foam fractionation and absorption techniques. Characterization studies will employ electrophoresis, diffusion, ultracentrifugation, sedimentation, velocity and equilibrium, selective adsorption and solubility studies to provide data on molecular size and structure.

(c) Patient material will not be used for this project initially except for urine specimens from NINDB patients admitted to other projects.

(d) Major Findings: In preliminary experiments, abnormally high concentrations of oxyproteic acids were isolated from the urines of patients with muscular dystrophy. Such patients also showed an abnormal loss or metabolism of injected human serum albumen tagged with radioactive I^{131} (see NINDB-). Since oxyproteic acids are thought to be intermediates in the breakdown of albumen, these two findings may be closely related and of significance to the disease.

More detailed studies have been delayed pending delivery of equipment on order for this project.

(e) Significance of this project: This is a more basic type of study designed to shed some light on certain complex molecules. The oxyproteic acids occur normally in urine as products of in vivo degradation of proteins, especially albumen. No detailed study or characterization of these compounds has ever been reported. In neuromuscular diseases there is degradation of nerve and muscle tissue, apparently associated with increased excretion of oxyproteic acids. A comparison of excretion by normal persons and those with muscle disease in regard both to quantity and quality would be of considerable significance.

Similarly, pyrogens have been shown to be associated with inhibition of glial scarring in central nervous system regeneration. The physical and chemical properties of such compounds are poorly understood and their mechanisms of action remain obscure. Elucidation of some of these factors should prove of value not only in pyrogen therapy but also in the more fundamental problem of fever mechanisms.

(f) Proposed Course: To initiate full scale studies outlined under methodology.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB- 19 (C)
SERIAL NO.

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11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENTS DAYS
FY 1956		2	1	3	0.2	0.2	0.4	0
FY 1957		2	1	3	0.2	0.2	0.4	0

12. BUDGET ACTIVITY

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 OR 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

Laboratory of Neuroanatomical Sciences, NINDB-Dr. Windle
(Serial No. NINDB-5 (L) 1954)

Clinical Investigations Division, NINDB-Dr. Shy
(Serial No. NINDB-3(C)-1954).

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH).

None.

R.P.C. - 3
December 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-19 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

None.

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

None.

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Medical Neurology
LABORATORY OR BRANCH

Clinical
3. Neurochemistry
SECTION

4.
LOCATION(OTHER THAN BETHESDA)

5. NINDB-20 (C)
SERIAL NO.

6. Quantitative, Microchemical Determination of Acetylcholine in Biological Specimens.
PROJECT TITLE

7. Dr. William C. Curtis and Dr. Donald B. Tower
PRINCIPAL INVESTIGATORS

8 Mr. Edmund L. Peters and Mr. John Phoenix
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

(a) Objectives: To adapt and develop a specific, quantitative chemical method for the determination of acetylcholine in brain tissue and fluids.

(b) Methodology: The finding by Neu (Ztschr. f. anal. Chemie 143: 30-38 (1954) that in the presence of tetraphenyl diboronoxide and a flavonol as little as 0.1 µg of acetylcholine can be detected as a colored precipitate or as red fluorescence in ultra-violet light suggested the possibility of adapting this observation to a chemical method for determination of acetylcholine. As reported by Neu (op. cit.), when quercetrin was used as the flavonol acetylcholine, but not choline, reacted. Investigation of this possibility is underway.

(c) Patient Material: None contemplated at this time.

(d) Major Findings: The reagent tetraphenyl diboronoxide is not commercially available. Successful synthesis of this compound from sodium tetraphenylborate by the method of Neu has been accomplished. Considerable difficulty has been experienced in obtaining pure samples of the various flavonols required for studying the reaction. Purification of crude samples of quercetrin was accomplished but no colored reaction product obtained. In checking with Neu he discovered that a trace of quercetin in the quercetrin is required to obtain a colored reaction product. This finding raises a question regarding the specificity of the reaction for acetylcholine in the presence of choline and may neccessitate chromatographic separation of the two compounds before carrying out the reaction.

(e) Significance of this project is most important and fundamental. No satisfactory chemical method for determination of microgram quantities of acetylcholine in biological specimens has ever been developed. Bioassay procedures are tedious, somewhat non-specific and often not sufficiently sensitive. In view of the importance of acetylcholine as a peripheral and also probably as a central transmitter of nerve impulses, there is a pressing need for better assay methods. This need is reinforced by the recent development by Udenfriend of a very satisfactory chemical method for Serotonin, a probable second transmitter in the central nervous system. Positive chemical idenfitication of acetylcholine in nervous tissue has only been reported twice in 35 years. There is need for re-assessment of acetylcholine with a specific chemical method particularly as more and more possible transmitters are proposed.

(f) Proposed Course of the project is to study the reaction in detail using a variety of flavonals (rutin, morin, quercetin, quercetrin, etc.) to determine its sensitivity, reproducibility and specificity. Depending upon the result of these studies adaptation of the method will then be attempted. The use of fluorimetric measurement of the final acetylcholine reaction product may require a red-sensitive fluorometer, which has been recently developed by Dr. Udenfriend (N.H.I.).

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-20 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1956		2	2	4	0.3	0.4	0.7	0
FY 1957		2	2	4	0.3	0.4	0.7	0

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATION PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 OR 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)(ITEM I)

National Heart Institute - Dr. Udenfriend.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES, OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH).

None.

R.P.C. - 3
December 1955

NINDB- 20 (C)
SERIAL NO.

15. NINDB-_____
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

None

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

None.

R.P.C. - 1
December 1955 Analysis of NIH Program Activities

Project Description Sheet

1. N.I.M.H. and N.I.N.D.B. 2. Lab Research (NIMH) and Medical Neurology (NINDB)
INSTITUTE LABORATORY OR BRANCH

3. Section on Cerebral Metabolism (NIMH)
Section of Clinical Neurochemistry (NINDB)
SECTION

4. ______________________________
LOCATION (OTHER THAN BETHESDA)

5. NINDB-21 (C)
SERIAL NO.

6. Cerebral Circulation in Minor Seizures.
PROJECT TITLE

7. Dr. Louis Sokoloff (NIMH) and Dr. Charles E. Wells (NINDB)
PRINCIPAL INVESTIGATORS

8. Dr. Donald B. Tower (NINDB) and Dr. C. Ajmone-Marsan (NINDB)
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

(a) Objective: To measure cerebral blood flow in patients with minor cerebral seizures (petit mal type) during hyperventilation and during the occurrence of seizures.

(b) Methodology: Cerebral blood flow studies will be performed using the radioactive Krypton (Kr^{79}) method devised by Lewis, Sokoloff, Wentz, Wechsler, and Kety (Fed Proc. 14:92 (1955)) and used extensively by Dr. Sokoloff during 1954-1955 at the U.S. Naval Air Development Center, Johnsville, Pa.

Concentrations of radioactive Kr^{79}, not exceeding 100μC./L., will be breathed from a closed spirometer reservoir by the subject through a tightly fitting mask for a period not exceeding 20 minutes. With this method readings over the cerebral hemispheres with an extensively shielded scintillation counter will be possible about every 30 seconds. Simultaneously arterial and cerebral venous blood samples will be drawn for Kr^{79} content. From these data and the Fick principle cerebral blood flow can be calculated.

Cerebral blood flow will be determined by this technique in the resting state, during hyperventilation and during seizures induced by hyperventilation, photic stimulation or other suitable means. Simultaneous electroencephalograms will be recorded wherever possible.

Arterial and cerebral venous blood samples will be analyzed for p CO_2, CO_2 content and pH and for oxygen saturation during these studies.

(c) Patient Material: Patients with suitable seizures will be admitted to NINDB wards for this study.

(d) Major Findings: This project will begin in calendar 1956. The procedure has been studied and perfected over several years at the Johnsville Air Development Center under Dr. Sokoloff's direction and the radiation problems and hazards carefully worked out and approved at that laboratory. The proposal has been submitted to the Clinical Center Radiation Committee for approval.

(e) Significance of this Project: The nitrous oxide method for measurement of cerebral blood flow requires a 10 minute observation, i.e. averaging of flow/min. over a 10 minute period. It is known from this method that hyperventilation in normal subjects and patients with generalized seizures (inter-ictal) results in decreased cerebral blood flow and that generalized seizures induced in monkeys result in marked increases in cerebral blood flow. No studies have been reported on effects of hyperventilation in patients with minor seizures (petit mal type) although it is this group which is most susceptible to the ictogenic effect of hyperventilation. In addition the relationship between cerebral blood flow and seizures has not been studied during actual seizures in man because of the time limitation imposed by the nitrous oxide method. With the radio krypton method accurate recording of such information would be of great fundamental significance.

(f) Proposed Course: To implement the above project.

R.P.C. - 2
December 1955

NINDB-21 (C)
SERIAL NO.

10. NINDB-
SERIAL NO.

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11. BUDGET DATA:

		ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
			PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1956	NINDB		2	2	4	0.15	0.2	0.35	100
	NIMH		1	1	2	-	-	-	0
FY 1957	NINDB		2	2	4	0.15	0.2	0.35	100
	NIMH		1	1	2	-	-	-	0

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12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 OR 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM I)

NIH-Radiation Safety Office
Massachusetts Institute of Technology-Cyclotron Production of Radioactive Krypton.

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH).

Nitrous oxide technique for measuring Cerebral Blood Flow and Oxygen Consumption - 1954 NIMH-16.

Cerebral Blood Flow Changes in Arial Maneuvers, measured by Radio Krypton-1954-NIMH-17.

R.P.C. - 3
December 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB- 21 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

None.

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

None.

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE
Clinical

2. Medical Neurology
LABORATORY OR BRANCH

3. Neurochemistry
SECTION

4.
LOCATION (OTHER THAN BETHESDA)

5. NINDB- 22 (C)
SERIAL NO.

6. Investigation of Vitamin B-12 Levels in Spinal Fluid
PROJECT TITLE

7. Dr. Charles E. Wells
PRINCIPAL INVESTIGATOR(S)

8. Dr. Guenther R. Haase and Dr. Donald B. Tower
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

(a) Objective: To determine the normal spinal fluid levels of Vitamin B-12 in health and disease and to determine whether when given in large doses the vitamin is concentrated in the spinal fluid.

(b) Methodology and Patient Material: Clinical material will be normal volunteer subjects and patients with a variety of neurological diseases (especially diabetes with neuropathy, pernicious anemia with combined system disease and the other peripheral neuropathies). Spinal fluid B-12 levels will be measured in these patients to determine the usual levels in normal patients and patients with neurological diseases. These subjects will then be given large doses of Vitamin B-12 parenterally for a period of one week (varying from 1,000 to 5,000 micrograms per day). At the end of this period a repeat lumbar puncture will be performed and the level of Vitamin B-12 will again be determined. It is hoped that in one or two normal subjects and in several patients it will be possible to do several lumbar punctures within the treatment period to determine a curve for the spinal fluid levels of the vitamin. Where practical vitamin levels in the blood will also be performed before and at the end of therapy. The Vitamin B-12 Assays will be carried out by the Lactobacillus microbiological method and will be performed initially at least by Merck and Co.

(c) Major Findings: This project began in December 1955. Two patients have been run through the plan outlined above but reports of the results are not yet available.

(d) Significance to Neurological Research: It is anticipated that spinal fluid levels of B-12 may rise considerably over a week's period with large doses of the vitamin, in contradistinction to the blood levels with such therapy. If such is the case, it would be of significance in determining the dosages to be employed in therapy with Vitamin B-12 and perhaps of more significance in demonstrating that the substance itself is concentrated within the spinal fluid.

(e) Proposed Course: To carry out studies outlined above.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB- 22 (C)
SERIAL NO.

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11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1956		2	2	4	0.15	0.2	0.35	*
FY 1957		2	2	4	0.15	0.2	0.35	

*Patients drawn from other NINDB project.

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12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 OR 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM L)

Research Division, Merck and Co., Rahway, N.J., Dr. George Boxer

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH).

None.

R.P.C. - 3
December 1955

Analysis of NIH Program Activities

Honors, Awards, and Publication Sheet

15. NINDB- 22 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

None

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

None.

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. N.I.N.D.B. — INSTITUTE
2. Medical Neurology — LABORATORY OR BRANCH
2. Clinical Neurochemistry — SECTION
4. ______ — LOCATION (OTHER THAN BETHESDA)
5. NINDB- 23 (C) — SERIAL NO.
6. Textbook of Clinical Neurochemistry — PROJECT TITLE
7. Dr. Donald B. Tower — PRINCIPAL INVESTIGATOR
8. Dr. Maynard Cohen, (University of Minnesota) — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

(a) Objective: Writing of a book covering the aspects of neurochemistry of importance to the clinical neurologists and others in the field of neurology who may possess insufficient biochemical background yet wish to obtain a general grounding in this field.

The book is intended to be 300-500 pages in length and to cover in as simple, diagrammatic terms as possible the major biochemical facts and views relating to the central and peripheral nervous systems and their correlation where known with clinical problems.

(b) Significance: There have been three books on neurochemistry in the past 50 years. Thudichum's Chemical Constitution of the Brain first published 75 years ago appeared in revised form in German in 1901. This is a classic and contains much data still of value regarding the gross chemical make-up of gray and white cerebral tissue. In 1937 Page published a monograph on Chemistry of the Brain which br brought Thudichum's data up to date and included what was then known of metabolism in brain tissue. This also is a classic but is much out of date, particularly regarding neuronal metabolism. In 1955 Elliott, Page and Quastel published Neurochemistry, a collection of 32 chapters by 32 authors covering most of the field. This book is actually valid up to 1951 only so that it is already somewhat behind current advances. In addition it is written primarily by and for investigators with biochemical background and not presented in any but the loosest organization. With a few exceptions there is little reference to clinical problems. The field of neurochemistry is experiencing growing interest from many areas of neurology, especially those in clinical neurology. A relatively short and moderately priced book directed to this latter group and organized in a logical basic to clinical progression will fill a much needed place.

(c) Proposed Course: The collaboration of Dr. Maynard Cohen, in charge of Clinical Neurochemistry at the University of Minnesota, has been secured. The medical Publishing House of Paul B. Hoeber, Inc., New York has contracted to publish the book. As a result of preliminary review a short synopsis of some of the salient features of cerebral metabolism has been presented at a Symposium Interdisciplinary Research, University of Wisconsin and will be published in 1956. A one-day course on neurochemistry will be given by the investigators at the April 1956 meeting of the American Academy of Neurology. These two events will permit the authors to assess the approach most suitable for the intended "non-biochemical" audience. It is anticipated that the manuscript for the book can be completed by the end of calendar 1956.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB- 23 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1956		1	1	2	0.2	0.1	0.3	0
FY 1957		1	1	2	0.1	0	0.1	0

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 OR 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)S (ITEM I)

University of Minnesota, Division of Neurology - Dr. Cohen
Paul B. Hoeber, Inc., New York - Publisher

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH).

None.

15. NINDB-______
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR 1955:

Tower, D. B. "Neurochemical Substrates of Cerebral Function and Activity" in H. F. Harlow and C. N. Woolsey, Symposium on Interdisciplinary Research in the Biological, Biochemical and Behavioral Sciences, Madison, University of Wisconsin Press, In Press.

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955.

None.

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Medical Neurology
LOCATION OR BRANCH

3. Clinical Neurophysiology
SECTION

4.
LOCATION

5. NINDB - 24 (C)
SERIAL NO.

6. Effect of temperature on neuromuscular transmission
PROJECT TITLE

7. Paul O. Chatfield, M.D.
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATOR(S)

9. PROJECT DESCRIPTION

OBJECTIVES:

This research is a combination of a project started in 1954, when it seemed desirable to study the effects of temperature on neuromuscular transmission, both from the standpoint of general physiological interest and because some clinical states of neuromuscular disorder are adversely affected when the patient is exposed to the cold. A review of the literature since carried out has revealed that the latter effect may be largely subjective.

METHODS EMPLOYED:

Hamsters are induced to hibernate by being kept in a cold room at 4° C. The anesthetized experimental animal (rat, hamster) or unanesthetized hibernating hamster is placed in a refrigerated box within which the temperature can be lowered a chosen amount (about 2 degrees centigrade in these experiments). The temperature of this box is thermostatically controlled so that it remains relatively constant. A sciatic nerve is exposed, placed upon stimulating electrodes and ligated, and crushed proximal to the electrodes. The gastrocnemius muscle of the same leg is freed from its insertion at the ankle and its tendon attached to a strain gauge for isometric

METHODS EMPLOYED, Cont'd.

recording of muscular contraction. The potential changes from the strain gauge are led into a DC amplifier and then recorded photographically with a cathode ray oscilloscope. Two fine wire electrodes are also inserted into the muscle and after suitable amplification the gross muscle action potential is recorded on the second beam of the oscilloscope. These electrodes are also used to stimulate the muscle directly. The temperature of the muscle was originally measured with a thermocouple leading into a bridge circuit and recording galvanometer. A Brown recording potentiometer is now used for this purpose. In this way the mechanical and electrical events occurring in the muscle as the result of stimulation of the sciatic nerve can be studied as a function of the temperature of the muscle.

MAJOR FINDINGS

During the past year further pilot experiments were done in this project, using the rat as a test animal. Preliminary results have confirmed information already available, to wit that a lower frequency of stimulation is necessary to obtain a complete tetanus in a cool muscle than in one at normal body temperature. The relation of tension to temperature is a complex one and demands further analysis. There seems little relationship between the amplitude of the electrical response and the tension developed, and the necessity of recording the electrical events as a function of temperature has been questioned.

SIGNIFICANCE OF THE PROGRAM TO THE INSTITUTE

Since one of the major interests of this institute is the large and varied group of diseases of the neuromuscular system and since some of these disorders are allegedly affected by cold, it seems of interest to try to define more clearly the exact effects which temperature has on neuromuscular function.

PROPOSED COURSE OF PROJECT

It is planned to amplify the experiments which have already been performed on the rat and to continue these studies on hamsters arousing from hibernation, i.e. those automatically changing their body temperature from low to high values as well as in anesthetized non-hibernating hamsters whose body temperature can be altered over a wide range without the procedure being lethal to the animal. It is planned to study the effects of temperature on muscular contraction brought about both by stimulating the nerve to the muscle and the muscle directly. Since the method of recording muscular contraction in use has not proved entirely satisfactory, improved methods probably utilizing different apparatus will be sought for.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB - 24 (C)
SERIAL NO.

11.
BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1956	$5,775	1	1	2	0.2	0.7	0.9	
FY 1957	$5,775	1	1	2	0.2	0.7	0.9	

12. BUDGET ACTIVITY:

RESEARCH X
ADMINISTRATION
REVIEW & APPROVAL
TECHNICAL ASSISTANCE

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. IF WITHIN NIH)

R.P.C. - 3
December 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB - 24 (C)
SERIAL NO.

16. None
LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

17. None
LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Medical Neurology
LOCATION OR BRANCH

3. Clinical Neurophysiology
SECTION

4. ______
LOCATION

5. NINDB - 25 (C)
SERIAL NO.

6. Effect of temperature on the electrophysiology of the visual system.
PROJECT TITLE

7. Paul O. Chatfield, M.D.
PRINCIPAL INVESTIGATOR

8. Wade H. Marshall
OTHER INVESTIGATOR(S)

9. PROJECT DESCRIPTION

OBJECTIVES:

Since the hamster during arousal from hibernation does not appear to respond to visual stimuli until its body temperature has regained fairly high levels, we propose to study the electrical responses of various parts of the visual system (e.g. lateral geniculate body and visual cortex) to light flashes directed at the retina. It is planned to carry out this research in the laboratory of Dr. Wade H. Marshall of the NIMH who has had considerable experience with this sort of research.

METHODS EMPLOYED:

Hamsters are induced to hibernate by being kept in a cold room at 4° C. They are then rapidly transferred to a refrigerated box, placed in a stereotaxic apparatus and the calvarium opened. Light flashes are directed at an eye while various portions of the visual system are explored according to ordinary electrophysiological techniques by means of the stereotaxic apparatus and records are made with a cathode ray oscillograph. Following each experiment the brains are fixed and later sectioned for localization of electrode positions.

R.P.C. - 1 a)
December 1955

NINDB - 25 (C)
SERIAL NO.

MAJOR FINDINGS

This project has just been started with the modification of an existing stereotaxic apparatus to fit the skull of the hamster. Further active research has had to be postponed for three months since Dr. Marshall is at present occupied with other research in collaboration with Dr. Aristides Leao, a Visiting Scientist.

SIGNIFICANCE OF THE PROGRAM TO THE INSTITUTE

It is felt that by studying the electrophysiology of the visual system, about which a great deal of information is already available, while varying the perameter of the body temperature of the animal, further information of interest may be obtained of interest both to neurophysiologiests and opthalmologists.

PROPOSED COURSE OF PROJECT

Outlined under "Methods".

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB - 25 (C)
SERIAL NO.

11.
BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS PROF	OTHER	TOTAL	MAN YEARS PROF	OTHER	TOTAL	PATIENT DAYS
FY 1956	$2000	1	1	2	0.2	0.7	0.9	
FY 1957	2000	1	1	2	0.2	0.7	0.9	

12. BUDGET ACTIVITY:

RESEARCH X	ADMINISTRATION
REVIEW & APPROVAL	TECHNICAL ASSISTANCE

Research will be in collaboration with the laboratory of neuro- (physiology,NIMH

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1955 or 1956: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. IF WITHIN NIH)

R.P.C. - 3
December 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB - 25 (C)
SERIAL NO.

None
16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

None
17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

December 1955 Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness — INSTITUTE
2. Medical Neurology — LABORATORY OR BRANCH
3. Clin. Neuropharmacology — SECTION
4. LOCATION (OTHER THAN BETHESDA)
5. NINDB-26(C) — SERIAL NO.

6. Study of new chemical compounds with central nervous system effects. — PROJECT TITLE

7. Richard L. Irwin, Ph.D. — PRINCIPAL INVESTIGATOR

8. None — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

OBJECTIVES: The study of pharmacologically active compounds that at first appear to be scientific curiosities is of importance for several reasons. Firstly some compounds of this type, when adequately characterized chemically and pharmacologically, find a useful place in therapeutics. Such substances have in the past also served as valuable research tools and have led to a greater understanding of physiological and biochemical mechanisms of disease processes. The objective of this project is to find compounds with central nervous system effects that have not been described and to investigate these compounds and others that have unusual or unexplained effects upon the central nervous system.

METHODS EMPLOYED: No method is known that will with certitude uncover pharmacologically active chemical substances. This project to date has been concerned with a search into folklore, anthropological literature and older scientific publications for reference to substances with pharmacologic activity that have not been previously or adequately investigated. Standard pharmacological procedures will be used when such substances are found and obtained.

MAJOR FINDINGS: To date reference to two substances have been found that are of interest. One of these compounds is reported to cause "madness" and is known as Felazlaz by some native peoples of the Sahara desert. Another reference to this compound indicated the name to be "Tebinna". Another group of compounds that have profound central nervous system effects that have received little attention is the Harmine alkaloids. These have been used as euphorics by Siberian peasants and have excitatory effects in animals that seem to be referable to the basal ganglia.

SIGNIFICANCE TO PROGRAM OF INSTITUTE: See objectives. This project is perhaps of more general interest than specifically related to an institute program.

PROPOSED COURSE OF PROJECT: To obtain, if possible, a supply of "Tebinna" (Felazlaz) and the harmine alkaloids for pharmacological testing and to continue the search for other active compounds.

R.P.C. 2
December 1955 Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB - 26 (C)
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: RESEARCH

13. NONE

14. NONE

Honors, Awards, and Publications Sheet

15. ______
SERIAL NO.

16. PUBLICATIONS OTHER THAN THIS PROJECT DURING 1955.

NONE

17. HONORS AND AWARDS TO PERSONNEL DURING 1955.

NONE

R.P.C. 1
December 1955 Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness — INSTITUTE
2. Medical Neurology — LABORATORY OR BRANCH

3. Clin. Neuropharmacology — SECTION
4. ______ — LOCATION (OTHER THAN BETHESDA)
5. NINDB-27 (C) — SERIAL NO.

6. A study of respiratory and vasomotor responses to central nervous system asphyxia. — PROJECT TITLE

7. Richard L. Irwin, Ph.D. — PRINCIPAL INVESTIGATOR

8. Jay F. Wells, M.S. — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

OBJECTIVES: To determine respiratory and vasomotor responses to asphyxia restricted to the central nervous system.

METHODS EMPLOYED: Responses were measured in anesthetized mammals using a vascularly isolated head in which neural connections remained intact.

MAJOR FINDINGS: The following observations were obtained from 22 dogs with vascularly isolated heads. The sudden occlusion of all arterial channels except the anterior spinal artery does not effect either vasomotor or respiratory function. When the anterior spinal artery is included in the occlusion an immediate vasopressor response ensues. This response is variable and is accompanied in some animals by cardiac arrhythmias. After an initial hyperpnea and polypnea, the occurrence of apnea, at approximately one minute after occlusion, was a constant finding in all dogs. When once established, apnea continued as long as the arterial channels remained occluded. When the arterial vessels were opened and blood flow resumed within ten minutes after the onset of apnea respiratory function returned to the pre-occlusion pattern.

SIGNIFICANCE TO THE PROGRAM OF THE INSTITUTE: Central nervous system function in relation to oxygen deprivation and carbon dioxide accumulation is inadequately understood. The number of neurological disorders which have parameters of function related to anoxia, asphyxia and hypercarbia attest to the importance of this type of study.

PROPOSED COURSE OF PROJECT: No immediate continuation of this project is contemplated. Experiments to separate the role played by anoxia from that of hypercarbia would be an obvious sequel to this project.

R.P.C. 2
December 1955

Analysis of NIH Program Activities
Budget Data Sheet

10. NINDB - 27 (C)
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: RESEARCH

13. NONE

14. NONE

Honors, Awards, and Publications

15.
SERIAL NO.

16. PUBLICATIONS OTHER THAN THIS PROJECT DURING 1955.

NONE

17. HONORS AND AWARDS TO PERSONNEL DURING 1955.

NONE

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Medical Neurology
LABORATORY OR BRANCH

3. Clinical Neuropharmacology
SECTION

4.
LOCATION(OTHER THAN BETHESDA)

5. NINDB-28 (C)
SERIAL NO.

6. The antagonism of quarternary compounds to neuromuscular block.
PROJECT TITLE

7. Richard L. Irwin, Ph.D.
PRINCIPAL INVESTIGATOR

8. Jay B. Wells, M.S.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

OBJECTIVES: This project is concerned with screening quarternary compounds for "de-curarizing" activity in anticipation of finding a compound that will be clinically useful in the treatment of myasthenia gravis.

METHODS EMPLOYED: Appropriate standard neuromuscular preparations.

MAJOR FINDINGS: NONE

SIGNIFICANCE TO THE PROGRAM OF THE INSTITUTE: The pharmacological treatment of myasthenia gravis during the past 20 years has centered upon compounds that have a pronounced anticholinesterase activity. Compounds that exhibit anticholinesterase effects only, such as physostigmine and the alkyl phosphonates, although somewhat efficacious in the treatment of myasthenia, have a low margin of safety or produce pronounced undesirable side effects at a clinical dose level. When a compound has anticholinesterase activity and also a direct stimulating effect upon the motor end plate, such as neostigmin or Mestinon (R), the clinical effectiveness is increased. This type of compound, with two distinct modes of action, and other similar ones, are invariably quarternary ions. It is also known that some quarternary compounds produce neuromuscular block. The pathological defect in myasthenia has often been proposed to be the circulation of a metabolite that reduces neuromuscular transmission by attachment to motor end plate receptors. It is unknown however whether the beneficial effect of neostigmin is dependent upon the displacement of a neuromuscular blocking metabolite from the motor end plate receptors or whether prostigmin acts by partially depolarizing the end plate membrane which would allow a smaller amount of acetylcholine to depolarize the end plate to a threshold level.

It has been shown in this laboratory, as well as in others, that certain quarternary compounds that have little anticholinesterase activity are somewhat antagonistic to a neuromuscular block. Hexamethonium, a bis-quarternary salt, is the best known example. This compound and other quarternary substance have found no clinical application as antagonists to a neuromuscular block since they have pronounced ganglionic blocking action that precludes their use. In large doses they also exhibit a low grade neuromuscular blocking action. However, in homologous series of quarternary ions compounds usually exist which have little if any ganglionic or neuromuscular blocking activity. It is unknown whether these compounds have any antagonistic effect against a neuromuscular block. If a compound can be found that (1) has minimal ganglionic blocking action, (2) is capable of antagonism of a neuromuscular block and (3) has little affinity for acetylcholine receptors at the motor end plate then the possibility exists that such a compound would be beneficial clinically in the treatment of myasthenia. The feasibility of an active compound of this nature being of benefit is not precluded by the possibility that the pathological physiology of myasthenia gravis is not dependent on a circulating neuromuscular blocking metabolite since quarternary ions are also known to depolarize the motor end plate. If the myasthenic defect is, as has also been postulated, a deficiency in acetylcholine production, a quarternary compound that would partially depolarize the motor end plate would enable a smaller output of acetylcholine to effect adequate neuromuscular transmission.

This project, based on the above considerations, is part of the integrated muscle disorders program of this Institute.

PROPOSED COURSE OF PROJECT: To continue to test quarternary compounds for activity against a neuromuscular block.

Budget Data Sheet

10. NINDB- 28 (C)
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: RESEARCH

13. NONE

14. NONE

Honors, Awards, and Publications Sheet

15. ____________
SERIAL NO.

16. PUBLICATIONS OTHER THAN THIS PROJECT DURING 1955.

NONE

17. HONORS AND AWARDS TO PERSONNEL DURING 1955.

NONE

R.P.C. 1
December 1955 Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Medical Neurology
LABORATORY OR BRANCH

3. Clinical Neuropharmacology
SECTION

4.
LOCATION (OTHER THAN BETHESDA)

5. NINDB-29 (C)
SERIAL NO.

6. The development of a "myasthenic" animal for testing purposes.
PROJECT TITLE

7. Richard L. Irwin, Ph.D.
PRINCIPAL INVESTIGATOR

8. Jay B. Wells, M.S.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

OBJECTIVES: Myasthenia Gravis is a neurological disorder that somewhat resembles a state of chronic neuromuscular block. No adequate laboratory method has been described that will give information as to whether any drug will be effective in the treatment of myasthenia. The standard techniques to test for antagonism against a neuromuscular block are inadequate since the disease is not reproducible in a laboratory animal. The purpose of the present project is to develop a method for more accurate testing of drugs that may be of value in the treatment of myasthenia gravis.

METHODS EMPLOYED: The rabbit head drop method has been selected as a beginning point since this method is not complicated by either extraneous electrical stimuli or anesthesia. Rabbits have been chronically curarized in an attempt to reproduce somewhat the conditions found in the myasthenic patient and then tested for response to neuromuscular blocking compounds.

MAJOR FINDINGS: No suitable method has as yet been developed. The chronic curarization of rabbits by a depository preparation of d-tubocurarine did not appreciably alter the response of the animals to test doses of the same substance.

SIGNIFICANCE TO THE PROGRAM OF THE INSTITUTE: The development of a new method for screening compounds that would be pharmacologically active in the treatment of myasthenia would perhaps aid in finding substances of clinical value. If a method can be found to produce a "myasthenic like" state in a laboratory animal it is conceivable that new information may be obtained concerning the neuromuscular processes involved in myasthnia about which little is known at present.

PROPOSED COURSE OF PROJECT: The search for a new method to test substances that may be effective in the treatment of myasthenia gravis will be continued. Chronic "curarization" of test animals by substances that have a different mode of action from d-tubocurarine will be investigated. The possibility that the inhibition of choline acetylase *in vivo* will produce a test animal that is somewhat similar to a myasthenic patient will be investigated. An attempt will be made to find compounds that are choline acetylase inhibitors.

R.P.C. 2
December 1955 Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB 29 (C)
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: RESEARCH

13. NONE

14. NONE

Honors, Awards, and Publications Sheet

15. ______
SERIAL NO

16. PUBLICATIONS OTHER THAN THIS PROJECT DURING 1955.

NONE

17. HONORS AND AWARDS TO PERSONNEL DURING 1955.

NONE

R.P.C. 1
December 1955 Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Medical Neurology
LABORATORY OR BRANCH

3. Clin. Neuropharmacology
SECTION

4. ____
LOCATION (OTHER THAN BETHESDA)

5. NINDB-30 (C)
SERIAL NO.

6. Neuromuscular blocking compounds: Peripheral and respiratory action related to calcium, potassium, magnesium, carbon dioxide and anesthetic gases.
PROJECT TITLE

7. Richard L. Irwin, Ph.D.
PRINCIPAL INVESTIGATOR

8. Jay B. Wells, M.S.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

OBJECTIVES: To determine how changes in the concentration of physiological ions and respiratory or anesthetic gases are related to the phenomenon of neuromuscular block.

METHODS EMPLOYED: During the course of this project a method has been devised to measure the respiratory effects of neuromuscular compounds under conditions that approximate those under which this type of compound is useful. The method is not dependent on extraneous nerve stimulation or artificial respiration. Peripheral actions are determined in standard nerve-muscle preparations in the rat, guinea pig, cat, rabbit and dog using alternating direct and indirect stimulation of the muscle.

MAJOR FINDINGS: The administration of calcium is markedly antagonistic to the peripheral as well as to the respiratory effects of the neuromuscular blocking compound succinylcholine. This has been found not to be due to a direct effect of calcium on muscle fibers or to the release of adrenalin by calcium. Indirect evidence suggests that cholinesterase activation by calcium is not involved. Calcium not only antagonizes a pre-existing neuromuscular block but also decreases the depth and duration of the block when calcium is administered prior to the blocking compound. Hypercarbia reduces both the duration and depth of the neuromuscular block produced by succinylcholine. The antagonism occurs only when acidemia has existed prior to the onset of the block and is thus the result of some physiological change that develops during hypercapnia. Anoxia, at least within the physiological limits of the cardiovascular system, has been found not to effect a neuromuscular block.

SIGNIFICANCE TO THE PROGRAM OF THE INSTITUTE: Myasthenia Gravis and familial periodic paralysis are neurological diseases in which both derangement of neuromuscular transmission and changes in ionic concentration in the blood may be involved. Until more knowledge on the mechanisms of a neuromuscular block and its relation to ionic concentration is available the etiology and treatment of these diseases must necessarily remain empirical. It is therefore important to examine the phenomena of neuromuscular block in greater detail than is possible in the patients. The investigation of the neuromuscular block and the conditions which affect it is the problem with which this project is concerned.

PROPOSED COURSE OF PROJECT: The phase of the project concerned with succinylcholine, calcium and respiration is complete and is documented in manuscript form to be presented for publication. The next phase of this project will concern the effect of hypercapnia on the neuromuscular block produced by compounds which are not hydrolyzed by cholinesterases i.e. decamethonium and gallamine. The relationships between a neuromuscular block and ionic fluxes will be investigated.

R.P.C. 2
December 1955 Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-30 (C)
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: RESEARCH

13. NONE

14. NONE

Honors, Awards, and Publications Sheet

15.
SERIAL NO.

16. PUBLICATIONS OTHER THAN THIS PROJECT DURING 1955.

NONE

17. HONORS AND AWARDS TO PERSONNEL DURING 1955.

NONE

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Cerebral Palsy
LABORATORY OR BRANCH

3.
SECTION

4.
LOCATION

5. NINDB-31 (C)
SERIAL NO.

6. The Evaluation of New Muscular Relaxant Drugs in the Treatment of Cerebral Palsy.
PROJECT TITLE

7. J. Gordon Millichap, M.D.
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Project: The Evaluation of New Muscular Relaxant Drugs in the Treatment of Cerebral Palsy.

Objectives: (1) To establish reliable objective methods for the quantitative assessment of motor disturbance in children with cerebral palsy.

(2) To determine the value of new muscular relaxant drugs in the treatment of cerebral palsy.

Methods: Objective measurements are obtained of coordination, range, accuracy and rapidity of movement, muscle strength, maintenance of posture, and degree of involuntary movement. Test procedures include kymographic records of the effects of choreoathetoid movements on postural stability, dark ground photographic records of athetoid movements with timed exposure, Minnesota rate of manipulation and other manual dexterity tests, hand dynamometer, vital capacity, and maximum leg abduction measurements. Neurological, physical therapy and occupational therapy evaluations, speech recordings, and limited motion picture studies are obtained.

Measurements are repeated at three day intervals, and other evaluations are made during drug treatment in which controls are employed. Results are subjected to statistical analyses.

R.P.C. - 2
December 1955

NINDB-31 (C)
SERIAL NO.

Analysis of NIH Program Activities

Patients under study:

Total: 10 children

In-patients: 4
Out-patients: 6

Significance to the Cerebral Palsy and Pediatric Neurology Program: In patients with cerebral palsy, muscular relaxation and the reduction of involuntary movements are essential preliminaries to the development of voluntary muscle control and proper movement patterns. A muscular relaxant drug of proven value would be an important addition to the treatment of cerebral palsy, and an effective preventive of contractures and deformity.

Major Findings: Preliminary assessment of the results of screening studies in four patients suggests that the degree of motor disability is increased during treatment with Reserpine, and decreased by Flexin (2-amino-5-chlorobenzoxazole).

Proposed Course of Project: In view of the encouraging results with Flexin, the study will be extended to include a total of ten patients. They will be followed as out-patients.

R.P.C. - 3
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-31 (C)
SERIAL NO.

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11. BUDGET DATA:

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12. BUDGET ACTIVITY: RESEARCH

13.

Clinical Center Services (Rehabilitation Department).

14.

None.

R.P.C. - 4
December 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-31 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

None.

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

None.

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Cerebral Palsy
LABORATORY OR BRANCH

3. ____________
SECTION

4. ________
LOCATION

5. NINDB-32 (C)
SERIAL NO.

6. The Anticonvulsant Action of Carbonic Anhydrase Inhibitors.
PROJECT TITLE

7. J. Gordon Millichap, M.D.
PRINCIPAL INVESTIGATOR

8. ____________
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Project: The Anticonvulsant Action of Carbonic Anhydrase Inhibitors.

Objectives: (1) To determine the efficacy of acetazoleamide (Diamox) in the treatment of those seizures which are not markedly influenced by hyperventilation and acid-base changes. /It is generally postulated that Diamox influences seizure activity by means of the secondary metabolic acidosis consequent to the inhibition of renal carbonic anhydrase. However, in animal experiments, the drug has an anticonvulsant effect which is independent of its action on the kidney and which is correlated directly with the degree of inhibition of carbonic anhydrase in the brain (Millichap, J.G., Woodbury, D.M., and Goodman, L.S., 1955.) Control of seizures, other than those exacerbated by hyperventilation and alkalosis, should therefore be expected._/

(2) To confirm, by clinical experiment, the development of tolerance to Diamox which has been noted in animal investigations, and to determine the efficacy of ammonium chloride in the reduction of tolerance.

Methods: The results of Diamox therapy are correlated with the etiology, anatomical localization, and clinical and EEG patterns (including response to hyperventilation) of the seizures. Control medications and the double-blind-technique are employed, and the patients are reviewed at frequent intervals.

Patients Studied:

Total of 23 children.

In-patients: 2
Out-patient follow-up consultations: 120

Major Findings: (1) The effectiveness of Diamox has been established in the control of those major and minor seizures, not markedly influenced by acid-base changes.

(2) The development of tolerance, hitherto unreported, detracts from the practical value of Diamox as an anticonvulsant.

Significance to the Cerebral Palsy and Pediatric Neurology Program: In children with cerebral palsy, the control of seizures is an essential preliminary to effective specific therapy, and there is urgent need for controlled evaluations of new and less toxic anticonvulsant agents. A study of the mechanism of the anticonvulsant action of Diamox should lead to an understanding of the physiological role of carbonic anhydrase in the nervous system and its relation to seizure activity.

Proposed Course of Project: The relatively low brain/plasma concentration ratio of Diamox limits its anticonvulsant activity (Millichap et al., 1955.) As a result of this finding, a more potent inhibitor has been produced and, if suitable patients are readily available, the compound will be evaluated clinically.

R.P.C. - 3
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-32 (C)
SERIAL NO.

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11. BUDGET DATA:

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12. BUDGET ACTIVITY: RESEARCH

13.

None.

14.

None.

R.P.C. - 4
December 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-32 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

(1) Methods of Evaluation of New Anticonvulsant Compounds. (Submitted for publication).

(2) Observations on the Anticonvulsant Action of Diamox, a Carbonic Anhydrase Inhibitor. (In preparation).

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Cerebral Palsy
LABORATORY OR BRANCH

3. ______
SECTION

4. ______
LOCATION

5. NINDB-33 (C)
SERIAL NO.

6. Studies on the Pathogenesis of the Kernicterus Syndrome
PROJECT TITLE

7. J. Gordon Millichap, M.D.
PRINCIPAL INVESTIGATOR

8. ______
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: 1) To investigate the significance of bile staining of the brain in the production of the kernicterus syndrome. 2) To investigate the relation of liver insufficiency, hypoglycemia, hypothermia, and iron deficiency of prematurity to the development of kernicterus. 3) To determine possible methods of prevention.

Methods: 1) Respiration of rat brain slices, in the presence of bilirubin, is measured by use of the Warburg constant volume respirometer. The *in vitro* inhibitory effect of bilirubin is being studied in relation to a) the purity of the sample, b) temperature, c) pH and various constituents of the media, and d) the presence of iron and copper.

2) Rats with liver necrosis and hypoglycemia will be used in the investigation of the relation of liver insufficiency and hypoglycemia to the kernicterus syndrome. The production of kernicterus in these animals will be attempted by injection of bilirubin solutions, a procedure which has been found unsuccessful in normal rats. Respiration of brain slices from animals injected with bilirubin will be compared with that of animals not injected.

Preliminary Results: The inhibitory effect of bilirubin on brain homogenates *in vitro* (Day, R.L., 1955) has been demonstrated also on brain slices. To obtain this effect, however, it is necessary to use an unphysiological media at a strongly alkaline pH. Under more physiological conditions, a significant degree of inhibition has not yet been obtained, despite staining of the tissue.

Significance to Cerebral Palsy Research Program: Though the incidence of the kernicterus syndrome has been reduced by exchange transfusion, a causal relation between bilirubin staining of the brain and the neurological sequelae of neonatal jaundice has not been established. The toxic effect of bilirubin, demonstrated *in vitro*, may be non-specific, and other factors associated with liver insufficiency, such as hypoglycemia and high serum ammonia levels, may be more significant. So that a better understanding of the nature of cerebral palsy may be obtained, and from the point of view of prophylaxis, it is important to elucidate the true causal factors in this condition.

Proposed Course of Project: No change.

R.P.C. - 3
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-33 (C)
SERIAL NO.

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11. BUDGET DATA:

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12. BUDGET ACTIVITY: RESEARCH

13.

Section on Metabolism, Nutrition and Liver Disease, Laboratory of Biochemistry & Nutrition, Institute of Arthritis & Metabolic Diseases.

14.

None.

R.P.C. - 4
December 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-33 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Cerebral Palsy
LABORATORY OR BRANCH

3. ______
SECTION

4. ______
LOCATION

5. NINDB-34 (C)
SERIAL NO.

6. Etiological and Clinico-pathological Correlations in Cerebral Palsy.
PROJECT TITLE

7. J. Gordon Millichap, M.D.
PRINCIPAL INVESTIGATOR

8. Neuropathologist to the Collaborative Cerebral Palsy Project.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Project: Etiological and Clinico-pathological Correlations in Cerebral Palsy.

Objectives: 1. To correlate prenatal, natal and post-natal factors generally considered of etiological significance in cerebral palsy, with the clinical and pathological findings.

2. To determine the incidence of factors, other than neonatal jaundice, of possible significance in the etiology of the kernicterus syndrome.

Methods: (1) Records of the pregnancy, birth and preceding clinical history are obtained on cerebral palsy patients with a history of neonatal jaundice, and these will be compared with the records of all children referred for possible inclusion in other cerebral palsy research projects. Detailed examinations and investigations are performed, and suitable normal control patients will be studied similarly. So that the degree of reliability and completeness of the histories, consistent with a retrospective investigation, may be optimal, patients will be admitted to the study as soon after diagnosis as is possible.

Patients Studied:

Total: 24 children
Inpatients: 4
Out-patients: 20

Analysis of NIH Program Activities

Progress: Records have been obtained on 24 children with cerebral palsy, and assistance has been given in forming a cerebral palsy protocol which eventually will be employed in this study. The cooperation of local hospitals and health departments has been obtained for the referral of patients and records.

Significance to the Cerebral Palsy and Pediatric Neurology Program: More precise etiological and clinicopathological correlations in cerebral palsy should lead to a better classification and understanding of this condition. The investigation of the kernicterus syndrome will help to elucidate the clinical significance of the results of laboratory research concerning bilirubin and brain respiration. (C.P. Project No. 802).

Proposed Course of Project: No change.

R.P.C. - 3
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-34 (C)
SERIAL NO.

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11. BUDGET DATA:

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12. BUDGET ACTIVITY: RESEARCH

13.

None.

14.

None.

R.P.C. - 4
December 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-34 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Cerebral Palsy
LABORATORY OR BRANCH

3.
SECTION

4.
LOCATION

5. NINDB-35 (C)
SERIAL NO.

6. Precocious Puberty in Children with Cerebral Palsy.
PROJECT TITLE

7. J. Gordon Millichap, M.D.
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Project: Precocious Puberty in Children with Cerebral Palsy.

Objectives: To determine the relation of skeletal and sexual precocity to organic brain damage in children with cerebral palsy.

Methods: (1) Children with cerebral palsy are investigated for signs of precocious puberty. A general physical examination and an x-ray study for bone-age are performed on all patients and, in those with positive findings, the urinary excretion of ketosteroids and corticoids is estimated. An endocrinology consultation is obtained to exclude causes other than neurogenic.

(2) The anatomical localization of the cerebral lesion in the patients with precocious puberty is compared with that in cerebral palsy patients who show no signs of precocity.

Patients Studied:

Out-patients: 12

R.P.C. - 2
December 1955

NINDB-35 (C)
SERIAL NO.

Analysis of NIH Program Activities

Significance to the Cerebral Palsy and Pediatric Neurology Program: A knowledge of the relation of precocious puberty to the brain lesion in cerebral palsy would help to define cortical-hypothalamic connections, and the role of the cerebral cortex in endocrine function.

Major Findings: Of 12 cerebral palsy patients in this study, 5 showed definite evidence of precocity, and causes other than neurogenic were excluded.

Proposed Course of Study: Further patients will be studied as above and, in addition, patients with seizures and focal cortical lesions will be investigated.

R.P.C. - 3
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-35 (C)
SERIAL NO.

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11. BUDGET DATA:

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12. BUDGET ACTIVITY: RESEARCH

13.

Endocrinology Service, National Cancer Institute.

14.

None.

R.P.C. - 4
December 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-35 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

None.

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

None.

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
BRANCH

3. Neurosurgical Service
Experimental Neurosurgery
SECTION

4.
LOCATION

5. NINDB-36 (C)
SERIAL NO.

6. Mechanisms of Memory
PROJECT TITLE

7. Maitland Baldwin, M. D.
PRINCIPAL INVESTIGATOR

8. Laurence L. Frost, Ph. D., and J. M. Van Buren, M. D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To further our understanding of those functional representations within the temporal lobe of man and the higher primates which may subserve the mechanisms of memory.

Methods Employed: 1. Electrical stimulation of the human temporal lobe during operative exposure under local anesthesia.
2. Ablation of the temporal areas in higher primates.

Patient Material:

		No.	Average stay - days
Admissions:	Adult Male	20	5.75
	Adult Female	26	7.27
	Children Male	3	17.33
	Children Female	4	5.0

Outpatient:	Number of Patients	21
	Number of Visits	28

Major Findings: In four patients we have elicited responses which indicate that there may be neuronal patterns in the temporal lobe which subserve the memory mechanisms.

In six patients whose temporal lobes were ablated on one or the other side, we observed changes in the ability to record present experience. These changes were such that the patients could not describe or define immediate experience and in at least one of the cases included some disorientation in space. In these cases it is noteworthy that we ablated the most mesial temporal structures and that there was some evidence of damage of these structures on the side opposite to the surgical removal.

In all patients with chronic lesions in one or the other or both temporal lobes, there is some disturbance of the mechanisms which serve to provide awareness, attention, perception and analysis of the meaning

PROJECT DESCRIPTION (continued)

of present experience. These disturbances lead to a failure of recording of this present experience or they may also lead to an inaccuracy of recollection or an inaccurate recording of this experience.

We have ablated the temporal lobe on one or the other side in three chimpanzees. These animals are higher primates and observations based on their behavior are useful through analogy in the study of human behavior. In a previous report we described the first immediate results of these ablations which consisted of immature behavior. Despite this change in behavior the chimpanzees have relearned patterns essential to feeding, grooming and cage play, in one case at least. These further observations have been made over the period intervening between these reports.

Significance to Neurological Research: This project and those allied with it in the Section of Clinical Psychology, serve to provide some data on the physiological basis and perhaps on the structural basis for memory. A major effort is being directed towards the establishment of data which will provide an understanding of some of the structural bases for mental functions and therefore for mind.

Proposed Course of Project: We plan a continuation of our present study of those neuronal patterns in the temporal lobe which subserve memory. The combination of information derived from direct electrical stimulation of the temporal lobe in man with information derived from studies of humans and higher primates in which the temporal areas have been ablated should provide useful and perhaps significant information concerning the structural basis for mind.

Analysis of NIH Program Activities

Budget Data

10. NINDB-36 (C)
SERIAL NO.

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11. BUDGET DATA

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12. BUDGET ACTIVITY: RESEARCH

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13. NONE

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14. NONE

Honors, Awards, and Publications

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16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

Psychological Changes After Subtotal Temporal Lobectomy.
Maitland Baldwin, M. D. Neuro-Chirurgie (Paris) - in press.

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17. HONORS AND AWARDS TO PERSONNEL DURING 1955:

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
BRANCH

3. Neurosurgical Service
SECTION

4. ____________
LOCATION

5. NINDB-37 (C)
SERIAL NO.

6. A Vestibular Representation in the Temporal Lobe
PROJECT TITLE

7. J.M. Van Buren, M.D.
PRINCIPAL INVESTIGATOR

8. Maitland Baldwin, M.D. and B. Ralston, M.D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: This study is undertaken to define the anterior boundary of the nystagmogenic area of the temporal lobe in man. It has been shown since the early portion of the 20th Century that lesions in the hemisphere of man produce accentuation of the quick phase of caloric nystagmus toward the side of the lesion. It has been subsequently demonstrated by Carmichael and Hallpike that this quick phase predominance toward the side of the lesion occurs whether cold water is irrigated in the contralateral or warm water is irrigated in the ipsilateral ear. The latter authors have further shown that the area responsible for this change lies in the posterior temporal region.

Because of the availability of patients in whom a measured quantity of temporal lobe had been removed for epilepsy, it was decided to follow out these studies to determine the anterior border of the portion of the cerebral cortex which affects the ocular response to caloric stimulation of the ears.

Method Employed: Prior to temporal lobectomy, a control examination was carried out and the same examination repeated following removal of measured portions of the temporal lobe. This examination consisted in positioning the patient with the neck flexed 30 degrees, and irrigating the external ear canals for 30 seconds with water 7 degrees above and 7 degrees below body temperature. Using a stop watch, the time of regular nystagmus was measured from the time the irrigation of the ear canal was commenced. In this way, a roughly quantitative measurement was obtained, which could be compared in the pre and post-operative periods.

PROJECT DESCRIPTION (Continued)

Patient Material:

		No.	Average Stay - days
Admissions:	Adult Male	11	6.27
	Adult Female	11	6.18
	Children Male	3	17.0
	Children Female	3	3.0

Outpatient: Number of patients: 10
Number of visits: 10

Major Findings: Although all of the material has not been fully correlated it appears that removal of the anterior 6 centimeters of the temporal lobe as measured along the sylvian fissure does not cause the appearance of nystagmus. Lesions, however, in the posterior temporal region, in the few instances where this has been invaded at operation, have produced the findings as mentioned above.

Significance to Neurological Research: The previous studies of this phenomenon have been by the use largely of cerebral tumors or, in a few cases, large destructive vascular lesions. The final localization of the phenomenon was arrived at by the method of super-imposition of the lesions upon a brain chart. The inherent weaknesses of this type of material and method of examination are apparent. It has therefore been felt of use to review this data using a more precise and quantitative cerebral lesion in man. In particular, we have been able to determine the anterior limits of this nystagmogenic area in man in the temporal lobe.

Proposed course of the Project: The majority of the patient work has now been finished. What remains is a correlation of the findings with a detailed review of the operative data.

R.P.C. 2
Dec. 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB-37 (C)
SERIAL NO.

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11. BUDGET DATA:

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12. BUDGET ACTIVITY: RESEARCH

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13. None

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14. None

Honors, Awards, and Publications

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16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

None

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17. HONORS AND AWARDS TO PERSONNEL DURING 1955:

None

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
BRANCH

3. Neurosurgical Service
SECTION

4. ______________
LOCATION

5. NINDB - 38 (C)
SERIAL NO.

6. Visual Field Deficits Following Temporal Lobectomy
PROJECT TITLE

7. J.M. Van Buren, M.D.
PRINCIPAL INVESTIGATOR

8. Maitland Baldwin, M.D. and B. Ralston, M.D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: This study is directed toward the definition of the precise course of the visual fibers in the temporal lobe. The precise relationship between the fibers of the visual radiation passing anteriorly in the temporal lobe and the retinal areas which they supply has been previously worked out only in a gross manner by the use of patients with neoplasms of the temporal lobe.

The availability of patient material in which the temporal lobe has been removed for epilepsy offered a unique opportunity for the restudying of the problem in patients where the removal was made in a relatively quantitative fashion and in which the effects of inactivation by compression, as may be found about a cerebral tumor, could be eliminated.

Method Employed: Both prior and following operation the visual fields were examined both on the perimeter and on the tangent screen with a variety of test objects. Particular attention was paid to the density of the visual field defect. In each case this density was determined by the use of a test object as required up to 10 inches in diameter. The relationship of the quadratic field defect to macular vision was also carefully tested by the use of small white or small colored objects. The visual acuity in all cases was carefully tested. Every opportunity has been taken to reëxamine patients at a considerable period following temporal lobectomy to rule out changes due to post-operative swelling which might appear in examinations made within the first month following operation.

R.P.C. 1 (a)
Dec. 1955

NINDB - 38 (C)
SERIAL NO.

PROJECT DESCRIPTION (Continued)

Patient Material:

		No.	Average Stay - days
Admissions:	Adult Male	15	11.07
	Adult Female	13	6.46
	Children Male	3	17.0
	Children Female	1	3
Outpatient:	Number of patients:	10	
	Number of visits:	10	

Major Findings: A complete evaluation of the findings so far has not been made. A preliminary impression is that there may be two types of visual field deficits. The most common is that of a non-homonymous upper quadrantanopia in which the largest and most dense defect appears in the eye ipsilateral in the temporal lobectomy. There are a few instances, but instances which have appeared with sufficient frequency to suggest that they are not merely chance happenings, in which the quadrantic field defect has proved to be homonymous. In no instance has the visual acuity been affected.

Significance to Neurological Research: The use of non-expanding destructive lesions of the temporal lobe in man has provided an unusual opportunity for the study of defects of the optic radiation in this area. The demonstration of two probable types of visual field defects in this area have been made. The significance of this difference at the moment is not apparent.

The non-homonymous nature of the field defects requires explanation in a differing spatial orientation of the optic radiation fibers from the opposite sides of the retina in the temporal portion of the optic radiation. Since in many cases the temporal lobectomy is accomplished by removal of gray and white substance from about the ventricle rather than by transection of the ventricle itself, it may be that these ipsilateral retinal fibers lie more laterally in the optic radiation and thus are more prone to damage than are the fibers from the contralateral retina which could lie closer to the ventricle and therefore be farther from the area of surgical damage. An alternative explanation would lie in the fact that instead of a lateral lamination there is an anteroposterior lamination in that the ipsilateral retinal fibers lie farther anteriorly in the temporal loop of the optic radiation than do the contralateral fibers. In this way removal of the temporal lobe from anterior to posterior would tend to strike first the ipsilateral fibers, then the contralateral, and thereby explain the larger defect in the ipsilateral eye.

PROJECT DESCRIPTION (Continued)

Proposed course of the Project: On the basis of the above unanswered questions, particular care is being taken in present temporal lobectomies to determine the degree to which the removal is tangential to the optic radiation and to what degree it is actually across the optic radiation, thereby entering the ventricle. It is hoped by further observation of patients with more detailed operative notes as to the nature of the lesion that the above incongruity may be elucidated.

In addition to the above studies, made purely on a clinical and operative basis, studies are being undertaken to reconstruct the lateral geniculate body in two patients who had died following temporal lobectomy. In this way, a correlation between the anatomical changes and those found at clinical examination of the patient may be achieved.

R.P.C. 2
Dec. 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB - 38 (C)
SERIAL NO.

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11. BUDGET DATA:

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12. BUDGET ACTIVITY: RESEARCH

13.

None

14.

None

Honors, Awards, and Publications

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16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

None

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17. HONORS AND AWARDS TO PERSONNEL DURING 1955:

None

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
BRANCH

Neurosurgical Service
3. Experimental Neurosurgery
SECTION

4. ____________
LOCATION

5. NINDB - 39 (C)
SERIAL NO.

6. A Study of Functional Representation in the Amygdala of Man and the Higher Primates
PROJECT TITLE

7. Maitland Baldwin, M. D.
PRINCIPAL INVESTIGATOR

8. Laurence L. Frost, Ph.D., Charles D. Wood, M.S., and Shirley Lewis, R.N.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To further understanding of the functions and functional connections of this important nucleus in man and the higher primates.

Methods Employed: 1. The electrical stimulation of the amygdaloid nucleus in patients under local anesthesia during operative exposure of the temporal regions.

2. The electrical stimulation of the amygdaloid nucleus in higher primates during operative exposure of the temporal regions and as chronic preparations after implantation of deep electrodes.

3. Electrographic recording from the temporal, parietal, frontal and deep temporal regions during these electrical stimulations.

4. As a result of the electrical stimulation of the amygdaloid nucleus in higher primates we have evoked afterdischarges from the nucleus to distant structures. We have recorded the spread of these after-discharges in some cases.

Patient Material:		No.	Average Stay - days
Admissions:	Adult Males	18	5.61
	Adult Females	23	7.09
	Children Male	3	17.0
	Children Female	4	5.0
Outpatient:	Number of Patients	18	
	Number of Visits	20	

Major Findings: The technique which we developed last year has been employed for electrical stimulation of the amygdaloid nucleus in patients during operation under local anesthetic. With this technique we have

Major Findings (continued):
evoked responses in thirty-six cases. These responses are motor, postural and autonomic. The motor responses are movements of face, jaws and upper extremities. The postural responses are posturing of the upper and lower extremities. The autonomic changes which occur are alteration of respiration and there is some change in sweating as well.

We have explored this nucleus with Horsley-Clarke and newer techniques in chimpanzees as well. In these animals we have implanted electrodes and developed chronic preparations after implantation. We have demonstrated that the anterior commissure provides a significant pathway of transmission between these nuclei in the monkey, and in both the monkey and the chimpanzee we have again elicited movements of face, and jaw and autonomic changes as well as postural phenomena following these deep stimulations. There is a diffuse alteration in the cortical electrical activity which changes after the stimulation, and this is most marked in the parietal regions. During these stimulations we have observed the changes in behavior which occur. The most significant and frequent change is an alteration of consciousness which begins with the onset of stimulus and ends as it ends.

Significance to Neurological Research: The amygdaloid nucleus is an important and central mechanism within the temporal lobe. It has functions related to face and jaw movement, autonomic function, and behavior as well as the mechanisms of consciousness. We must understand it and its connections if we would understand temporal lobe epilepsy.

Proposed Course of Project: We are continuing the stimulation of this nucleus in man and in the primates. We will conduct a thorough study of its anatomical connections in the primates and we are studying the problems of behavior in man and the primates as well as the electrophysiological problems related to the stimulations in both man and the primates. Future studies of this kind should provide important information concerning the mechanisms of temporal lobe epilepsy and certain aspects of behavior and the mechanisms of consciousness.

R.P.C. 2
Dec. 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB-39 (C)
SERIAL NO.

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11. BUDGET DATA

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12. BUDGET ACTIVITY: RESEARCH

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13. NONE

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14. NONE

Honors, Awards, and Publications

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16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

Investigation of the Primate Amygdala: Movements of the Face and Jaws. II. Ablation and Afterdischarge. Neurology - in press. Maitland Baldwin, M. D., Laurence Frost, Ph.D., C. D. Wood.

Investigation of the Primate Amygdala: Afterdischarge and Anterior Commissure Studies. Pending. Laurence Frost, Ph.D.,Maitland Baldwin, M. D., C. D. Wood.

Epileptiform Discharge in the Primate Amygdala. Pending. Laurence Frost, Ph.D., Maitland Baldwin, M. D., C. D. Wood.

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17. HONORS AND AWARDS TO PERSONNEL DURING 1955:

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
BRANCH

Neurosurgical Service
3. Experimental Neurosurgery
SECTION

4.
LOCATION

5. NINDB-40 (C)
SERIAL NO.

6. Investigation of the Second Sensory Areas in Man
PROJECT TITLE

7. Maitland Baldwin, M. D.
PRINCIPAL INVESTIGATOR

8. J. M. Van Buren, M. D.
OTHER INVESTIGATORS

9. Project Description

Objectives: To outline the extent and nature of these sensory representations in man and if possible discover their functional significance.

Methods Employed:
1. Electrical stimulation of these areas under local anesthesia during operative exposure.
2. Recording of these results.
3. Electrographic recording during these stimulations.

Patient Material:

		No.	Average Stay - days
Admissions:	Adult Male	14	6
	Adult Female	17	5.82
	Children Male	3	17
	Children Female	7	9

Outpatient: Number of Patients: 17
Number of Visits: 19

Major Findings: We have evoked positive responses relative to second sensory areas in 53 patients. Some of these responses have been obtained from the upper bank and fissure of Sylvius, as well as the surface of the island of Reil. The latter category are infrequent, however. It is interesting that twelve of the cases showed sensory responses after stimulation of the lateral aspect of the first and second temporal convolution. These findings seem to indicate that there may be some sensory representation relative to this part of the temporal cortex. If this is true we have encountered yet another second sensory area. This area is as yet unreported and has not been described in the literature.

Significance to Neurological Research: This is a relatively unknown area of brain function. Knowledge of its function is important to our understanding of the sensory mechanisms of the brain and is essential to our knowledge of temporal lobe epilepsy since epileptogenic lesions often activate this area and their expression is not clearly understood.

Proposed Course of the Project: We must continue stimulations of these areas in man and reinforce the knowledge gained from these stimulations by evoked potential studies in the operating room. This work will be substantiated and reinforced by observations on the brains of higher primates as well.

With apparatus which we have developed in connection with another project, we will pursue these studies. This apparatus will permit us to evaluate the results of evoked potentials in these areas in both the human and chimpanzee. Such observations should provide more objective data and if this is forthcoming we may substantiate our observations concerning sensory representation in the temporal cortex.

R.P.C. 2
Dec. 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB-40 (C)
SERIAL NO.

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11. BUDGET DATA

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12. BUDGET ACTIVITY: RESEARCH

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13. NONE

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14. NONE

Honors, Awards, and Publications

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16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

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17. HONORS AND AWARDS TO PERSONNEL DURING 1955:

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
BRANCH

3. Neurosurgical Service
Experimental Neurosurgery
SECTION

4.
LOCATION

5. NINDB - 41 (C)
SERIAL NO.

6. An Investigation of the Autonomic Phenomenon which Follows Stimulation of the Temporal Areas in Man and the Higher Primates
PROJECT TITLE

7. Maitland Baldwin, M. D.
PRINCIPAL INVESTIGATOR

8. J. M. Van Buren, M. D., Laurence Frost, M. D., Charles Wood, M. S., Shirley Lewis, R. N.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To further understanding of the central representations of autonomic function.

Methods Employed:
1. Electrical stimulation at operation.
2. Electrographic and electronic recording during this stimulation.

Patient Material:

		No.	Average Stay - days
Admissions:	Adult Males	19	7.05
	Adult Females	19	5.63
	Children Male	3	17.0
	Children Female	5	5.6

Major Findings: In patients at operation under local anesthesia we have observed changes in blood pressure, pulse, respiration and gastric motility following stimulation of the insula; following stimulation of the amygdaloid nucleus we have observed changes in respiration and in pulse rate.

In chimpanzees and in monkeys we have observed similar changes.

Significance to Neurological Research: Central representation of autonomic function is not clearly understood. These central representations which we have outlined are important in the understanding of the structural basis of emotions and in the understanding of the central control of the cardiovascular and respiratory systems.

PROJECT DESCRIPTION (continued)

Proposed Course of Project: We must outline the exact nature of these autonomic changes which follow central stimulation in man. We have entered mechanisms which are important in neurology as well as in the understanding of changes in the cardiovascular and respiratory systems.

We will continue electrical stimulation of these areas in man and the higher primates and attempt to make our recording of the results more exact by additional techniques, both in man and the primates.

R.P.C. 2
Dec. 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB-41 (C)
SERIAL NO.

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11. BUDGET DATA

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12. BUDGET ACTIVITY: RESEARCH

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13. NONE

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14. NONE

Honors, Awards, and Publications

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16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

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17. HONORS AND AWARDS TO PERSONNEL DURING 1955:

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
BRANCH

3. Neurosurgical Service
Experimental Neurosurgery
SECTION

4.
LOCATION

5. NINDB-42 (C)
SERIAL NO.

6. A Study of the Evoked Potentials in the Somatosensory Cortex Following Stimulation of the Temporal Cortex (from peripheral stimuli and from stimuli applied to the surface of the temporal cortex).
PROJECT TITLE

7. Maitland Baldwin, M. D.
PRINCIPAL INVESTIGATOR

8. J. M. Van Buren, M. D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To outline the extent and nature of the somato-sensory representation in man and identify any functional relationship which may exist between it and the lateral temporal cortex.

Methods Employed:
1. Electrical stimulation of these areas under local anesthesia during operative exposure.
2. Recording of these results.
3. Electrographic recording during these stimulations.

Patient Material:

		No.	Average Stay - days
Admissions:	Adult Male	1	4
	Adult Female	1	6
	Children Male	0	
	Children Female	0	

Outpatient:	Number of Patients:	0
	Number of Visits:	0

Major Findings: During the period of this report we have developed an apparatus which will permit us to develop a peripheral stimulus and coordinate this development with cortical recording. It was necessary that this apparatus be developed as it is essential to the further pursuit of the objectives outlined for this particular project.

Significance to Neurological Research: The somato-sensory areas in man have not been outlined completely by evoked potential techniques. This is an essential step in the further understanding of this important area of functional representation within the cortex. There is no indication in present knowledge that the postcentral gyrus or somato-sensory

Significance to Neurological Research (continued)
cortex is related to the lateral temporal cortex, nor is there any indication in present knowledge that the lateral temporal cortex subserves sensory function. Some of our findings obtained in another project suggest that such function is subserved here and this project may assist us in a substantiation of this evidence.

Proposed Course of the Project: We will apply the apparatus which we have developed to further studies of the human and higher primate cortices in order to outline the somato-sensory area and analyze any relationships between it and the lateral temporal cortex which can be observed through the use of these particular techniques.

R.P.C. 2
Dec. 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB-42 (C)
SERIAL NO.

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11. BUDGET DATA

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12. BUDGET ACTIVITY: RESEARCH

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13. NONE.

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14. NONE.

Honors, Awards, and Publications

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16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

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17. HONORS AND AWARDS TO PERSONNEL DURING 1955:

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE
2. Surgical Neurology
BRANCH
Neurosurgical Service
3. Experimental Neurosurgery
SECTION
4.
LOCATION
5. NINDB - 43 (C)
SERIAL NO.

6. An Investigation of Speech Function Localized in the Temporal Areas of Man
PROJECT TITLE

7. Maitland Baldwin, M. D.
PRINCIPAL INVESTIGATOR

8. Laurence L. Frost, Ph. D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To outline the extent of cortical speech representation in man and to understand the relative significance of the areas outlined in speech functions.

Methods Employed: 1. Electrical stimulation of the temporal and parietal cortex in patients during operations under local anesthesia.
2. Clinical examination of speech function before and after such operations.

Patient Material:		No.	Average Stay - Days
Admissions:	Adult Male	24	9.67
	Adult Female	23	6.35
	Children Male	3	17.0
	Children Female	6	5.5
Outpatient:	Number of Patients	19	
	Number of Visits	23	

Major Findings: During the period of this report we have continued our outline of the speech representation in human cortex. It is interesting that in some of these cases speech representation does not appear on the side opposite to the writing hand and in others it appears on the same side as the writing hand.

Individuals with temporal lobe lesions seem to have some difficulty in speech regardless of the side of the lesion. In the majority of cases, this difficulty is marked and obvious when the lesion is related to the side of dominance or major speech representation. However, in other cases, where the lesion is on the side opposite to that of major speech representation, there is also a difficulty in speech. In the first and larger group of cases the speech difficulty falls within the well-defined patterns of aphasia. In the second group it is more subtle

PROJECT DESCRIPTION (continued)

and is concerned with the ultimate semantics of speech. These patients have difficulty with the use of words so as to properly define a meaning. This difficulty does not appear where the word which supports or defines the meaning is used alone; as for example, if the patient is asked to name "pencil" after being shown this object, he does so with ease, but if he is asked to use the word "pencil" in a sentence so as to describe this object he has difficulty. These patients find it difficult to use words in adequate relationships but can use individual words adequately as unit symbols, but they cannot use groups of words as accurate symbols of thought or description.

Significance to Neurological Research: Speech is among the most complicated functions of the human brain. We know little of its intrinsic mechanisms. Some knowledge of these functions provides great assistance to the neurologist in diagnosis of brain disease and in the rehabilitation of those with brain lesions. This project relates to the one on vestibular and auditory function and also to the psychological study of speech. In combination these projects should provide information of value to the neurologist, psychologist and psychiatrist.

Proposed Course of Project: We will continue along present lines and add more precise methods of testing speech in the operating room as well as methods designed to outline the cortical representations of hearing and vestibular function.

We are beginning to observe the fragments of speech which occur during some cases of automatic behavior and we will continue observations of this distorted expression. It is interesting that individuals who owe their automatism to temporal lobe lesions may speak during their periods of automatic behavior if the essential temporal lesion is on the side of major speech representation.

R.P.C. 2
Dec. 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB-43 (C)
SERIAL NO.

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11. BUDGET DATA

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12. BUDGET ACTIVITY: RESEARCH

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13. NONE.

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14. NONE.

Honors, Awards, and Publications

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16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

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17. HONORS AND AWARDS TO PERSONNEL DURING 1955:

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
BRANCH

3. Neurosurgical Service
Experimental Neurosurgery
SECTION

4.
LOCATION

5. NINDB - 44 (C)
SERIAL NO.

6. Studies of Involuntary Movements
PROJECT TITLE

7. Maitland Baldwin, M. D.
PRINCIPAL INVESTIGATOR

8. J. M. Van Buren, M. D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objective: There are certain diseases of the nervous system characterized by involuntary movements. At present, the precise cause of the majority of these debilitating conditions is unknown. Likewise, the precise action and sites of action of the various causal agents are not clear. However, the ultimate effects of many of these abnormal processes have been outlined. These effects have been analyzed through the various techniques of pathological anatomy.

If pathological anatomy can provide some definitive information, perhaps the correlation of these structural changes with clinical phenomena may provide further and equally useful information.

The most obvious clinical manifestation of these diseases is and has been the involuntary movements which seem to characterize their course.

Therefore, we have begun an analysis of these movements, with the hope that data thus acquired may be related to the definitive changes which have been reported as the ultimate effects of the disease processes.

In addition to our analysis of the involuntary movements, we hope to observe the changes in some of these movements which occur after certain accepted surgical treatments have been applied in selected cases.

Methods Employed:
1. Clinical Observation.
2. Photographic Techniques.
3. Analysis by illustration of movement phases.

Major Findings: The past year has been spent in the development of photographic and other means of illustrating the nature of involuntary movements in a small group of patients. This effort has provided us with a useful technique. In the use of this technique we find that the movements studied can be analyzed and this analysis indicates the essential characteristics of the movement pattern.

Major Findings (continued): In three cases we observed involuntary movements. It was necessary to remove the temporal lobe in each of these cases. This removal was followed by changes in the involuntary movements. Indeed, in two cases the movements ceased. In the other case, there was some change in the movements as well as in the rigidity.

Present knowledge does not serve to explain these findings. It may be that the amygdaloid nucleus has some relationship in the abnormal functions which underly some of these movement patterns.

Significance to Neurological Research: Diseases which cause involuntary movements are not understood and cannot be treated effectively. These studies will constitute one small step towards an increase in understanding.

Proposed Course of Project: The techniques of observation will be applied to selected patients and some of these patients will be treated by interruption of pathways which subserve motion. Wherever possible we will make anatomical analyses of the available material and correlate these findings with the clinical observations. Likewise we will begin correlation of this data with observations made in the laboratory on experimental animals.

Patient Material:

		No.	Average Stay - days
Admissions:	Adult Males	0	
	Adult Females	2	150
	Children Male	1	18
	Children Female	0	
Outpatients:	Number of Patients	1	
	Number of visits	1	

R.P.C. 2
Dec. 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB - 44 (C)
SERIAL NO.

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11. BUDGET DATA

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12. BUDGET ACTIVITY: RESEARCH

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13. NONE

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14. NONE

Honors, Awards, and Publications

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16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

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17. HONORS AND AWARDS TO PERSONNEL DURING 1955:

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
BRANCH

3. Neurosurgical Service
Experimental Neurosurgery
SECTION

4. LOCATION

5. NINDB-45 (C)
SERIAL NO.

6. Human Cortical Physiology
PROJECT TITLE

7. Maitland Baldwin, M. D.
PRINCIPAL INVESTIGATOR

8. J. M. Van Buren, M. D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To outline the extent and nature of functional representations in the cortex of man.

Methods Employed: 1. Electrical stimulation of the human cortex under local anesthesia during operative exposures.
2. Observation of the apparent effect of selected cortical ablations in man and higher primates.
3. Electrocorticographic recording during stimulation of the exposed human cortex and peripheral recording designed so as to analyze autonomic and motor responses which may follow this stimulation.
4. Electrical stimulation of the cerebral cortex in higher primates under analagous conditions with cortical and peripheral recording.

Patient Material:		No.	Average Stay - Days
Admissions:	Adult Male	22	9.86
	Adult Female	24	7.79
	Children Male	6	24.67
	Children Female	8	9.88

Outpatient: Number of Patients: 20
Number of Visits: 24

Major Findings: We have stimulated the human cortex in the frontal, temporal, parietal, and occipital regions. The majority of these stimulations have been undertaken under local anesthesia so that the subjective as well as objective responses might be observed and recorded. The majority of these stimulations have been undertaken over the wide area of the temporal cortex, since the majority of our cases suffer from temporal lobe lesions and the area of the lesion indicates the area of exploration and stimulation. We have elicited motor and sensory responses from the temporal cortex during the past year. These responses

PROJECT DESCRIPTION (continued)

which were evoked in man have also been tested in the laboratory and we have elicited motor responses from the temporal cortices of both monkeys and chimpanzees.

We have observed a change in cortical activity which seems to follow stimulation of the amygdala in the human and also in the chimpanzee. In the human, electrical stimulation of the amygdaloid nucleus is followed by a relative suppression of activity over the temporal and parietal cortices.

Significance to Neurological Research: Accurate observations of human cortical physiology have a wide clinical and scientific application. The analysis of these observations in terms of "brain maps" has served to integrate the various functions in terms of the entire cortex. Thus, through compilation of brain maps which summarize large numbers of responses, one may obtain ideas as to concentration of function within certain cortical areas.

Proposed Course of Project: We will continue the gentle electrical stimulation of the human cortex. During the coming year these stimulations will provide more data because we have now obtained new apparatus for the simultaneous recording of multiple peripheral responses and also we are now in a position to substantiate some of the information gained by direct cortical stimulation through the use of the evoked potential technique.

R.P.C. 2
Dec. 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB-45 (C)
SERIAL NO.

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11. BUDGET DATA

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12. BUDGET ACTIVITY: RESEARCH

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13. NONE.

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14. NONE.

Honors, Awards, and Publications

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16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

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17. HONORS AND AWARDS TO PERSONNEL DURING 1955:

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
BRANCH

3. Neurosurgical Service
Experimental Neurosurgery
SECTION

4.
LOCATION

5. NINDB-46 (C)
SERIAL NO.

6. Epileptogenic Mechanisms in the Brain of Man
PROJECT TITLE

7. Maitland Baldwin, M.D.
PRINCIPAL INVESTIGATOR

8. C. Ajmone-Marsan, M.D., J.M. Van Buren, M.D., Bruce Ralston, M.D., / D. B. Tower, M. D., and E. C. Alvord, M.D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To study causal mechanisms of epileptic seizures in man:
a. To study the characteristics of epileptogenic areas in the brain of man.
b. To study the characteristics of the lesions which predispose to epileptogenic changes in the brain of man.
c. To study the clinical expression of these epileptogenic areas in man.
d. To study the electrographic characteristics of epileptogenic activity in the brain of man.
e. To study the approved methods of surgical therapy for these lesions and develop new therapeutic methods.
f. To study brain function as it is exposed in the extravagant experiments devised by these lesions.

Methods Employed:
a. Clinical neurological examination.
b. Special radiographic examination.
c. Electrographic examination.
d. Electrocortigraphic examination.
e. Electrical stimulation of the lesion exposed at operation.
f. Selective isolation of the lesion at operation.
g. Cinematographic and sound recording.
h. Histological and chemical examination.

Patient Material:

		No.	Average stay - days
Admissions:	Adult Male	55	18.93
	Adult Female	48	20.17
	Children Male	23	42.65
	Children Female	19	21.26

Outpatient: Number of patients: 76
Number of visits: 124

PROJECT DESCRIPTION (Continued)

Major Findings: During the past year we have studied the motor and autonomic phenomena of temporal lobe seizures in the human and in the chimpanzee. From these studies we now conclude that an epileptogenic lesion in one or the other temporal lobe sooner or later expresses its presence through movements of face and jaws, and these movements also begin on the side of the lesion. Thus observation of the initial movements in a temporal lobe seizure may serve to lateralize the essential epileptogenic lesion. It seems clear that these movements become bilateral in the majority of cases but in the cases we have observed in the chimpanzees which we have used as experimental preparations, these movements began on the same side as the essential lesion.

In almost all patients and in the majority of experimental animals, a temporal lobe seizure actually begins with a change in the width of the palpebral fissures. This widening is bilateral and is soon followed by a change in pupillary size. Thereafter the movements of face and jaw begin. It may be significant that the face usually changes in color as the pupils dilate and before salivation occurs. Salivation actually occurs in most cases of temporal lobe seizures. The first salivation begins at the same time as the movements of the face. At this time the secretion is slight and the mixture is mucoid. As the attack continues the quality of the secretion changes and it becomes watery. These autonomic changes may be accompanied by another, which is an alteration in respiration. This usually occurs at the same time as the movements of face and jaw begin and it is an inspiratory arrest. All of these autonomic phenomena are significant, and we have reproduced them experimentally in the chimpanzee and observed them frequently in the sequence described as they occurred in our patient material.

Posturing of the upper extremities is characteristic of the expression of epileptic activity in one or the other temporal lobe. This usually begins on the side opposite to the lesion and it occurs after the movements of face and jaws and coincident with the second type of salivation. We use the term "posturing" because the involved extremity becomes hypertonic before any movement occurs, and subsequently movements either of hand or arm are superimposed on a posture of either flexion or extension.

Many temporal lobe seizures are characterized by automatic behavior. This behavior is either ictal or postictal, and indeed it is difficult to place it within the sequence of the attack. However, in our cases it has usually occurred at the end of the attack or is a continuation of an attack characterized by the phenomena which we have described above. In a very few of the cases the entire attack consists of this bizarre behavior. In some cases speech is an outstanding feature during this alteration of consciousness. These are cases in which the essential lesion lies in the temporal lobe

PROJECT DESCRIPTION (Continued)

on the side of major speech representation. This speech is expressed either as jargon or as sentences inappropriate to the immediate environmental circumstances. In one case the patient replied to a direct question. When he was asked what he was doing, he said he was looking for something. However, his search was fruitless and he did not speak again.

We have reproduced fragments of this bizarre pattern in chimpanzees and recorded it in color movies. This reproduction occurred after the establishment of an afterdischarge in one amygdaloid nucleus and subsequent to the production of movements of face and jaws, autonomic changes, and posturing phenomena which we have described above. The animal plucked at himself, looked about the room, and seemed to search for something.

In the surgical treatment of temporal lobe seizures, we have achieved a greater understanding of the significance of the deeper structures in the production of these seizures. We have observed cases at operation in which the abnormal discharges were recorded infrequently from the temporal surface and with increasing frequency as we approached the deeper structures in the surgical dissection. In these cases we have also had an opportunity to record directly from amygdala, hippocampus and hippocampal gyrus and these recordings have provided examples of the epileptogenic activity at its apparent source.

In the course of such dissections, we have been able to modify the original Penfield technique so as to facilitate this operative procedure.

We have tested the effects of hypothermia on epileptic discharge in the amygdaloid system in chimpanzees, and we have also tested the effect of hypothermia on epileptic discharge which originated in the supplementary motor area in one human case. In the experimental cases, hypothermia seemed to dampen this discharge and reduce its spread. In the human case, the hypothermia did not materially alter the activity of the epipeptogenic lesion. In the experimental animals we were dealing with the amydgaloid or limbic system, and in the human, with a more or less discrete cortical lesion lying on the lateral aspect of the convexity. It may be that this variation in effect gives some indication of variation in characteristics of these separate and distinct neuronal areas.

In seizure cases characterized by a spike-and-wave discharge, we have tested the effects of some of the drugs commonly used in the reduction of symptoms due to basal ganglia disease. These drugs seemed to alter the extent and range of the motor phenomena which characterized the expression of the spike-and-wave discharge. They did not alter the frequency of the attacks and in no way changed the fundamental alteration of consciousness which characterized each of

PROJECT DESCRIPTION (Continued)

these seizures.

We studied the effects of thorazine and serpasil in cases of temporal lobe and centrencephalic seizures. These drugs do not affect the frequency of attacks but they do tranquilize the patient.

We have observed the psychotic phenomena which sometimes accompany or occur as a result of epileptic discharge in one or the other temporal lobe. In three cases of temporal lobe seizures, we withheld anticonvulsant medication for a brief period. During this period each of these cases became confused, irrational, and incoherent. One case became aggressive and another patient showed unusual alteration in mood. In each patient there was evidence of psychosis and this was confirmed by competent psychiatric opinion. These psychological aberrations disappeared after resumption of anticonvulsant medication. They were coincident with epileptic discharges referable to one or the other temporal region.

In one case the frequency of the attacks was directly proportional to the degree of amnesia. This was a case of temporal lobe seizures in which the attack consisted entirely of a feeling of "having been there before". The deja vu phenomena was followed by a brief period in which consciousness was altered, the face changed color, the pupils dilated and the palpebral fissures widened. The entire duration of the attack never exceeded one minute. This patient's ability to record immediate and present experience, and at least her ability to recollect experiences of the immediate past, was radically altered by the frequency of these attacks. The number of attacks never exceeded five per day and they were usually widely spaced throughout a twenty-four hour period. As they decreased in frequency her recollective facilities improved and she was able to retain information derived from direct observation and audition. She could not retain this information adequately during the periods of frequent seizures.

In cooperation with the Department of Social Work we have begun and are continuing a study of the social factors which influence the family, community or institution which contain individuals who are epileptic.

In cooperation with the section of Clinical Psychology we are studying and have studied personality characteristics in these cases.

Significance to Neurological Research: The clinical observations which we have described above may be significant in the localization and lateralization of temporal lobe lesions which are epileptogenic. They also serve to further our understanding of functional representation within the human and higher primate temporal lobe. The effects of hypothermia on the epileptogenic lesion in the limbic system have been not noted previously. The fact that hypothermia seems to suppress epileptogenic discharge in this system and leaves it unaltered or

PROJECT DESCRIPTION (Continued)

actually accelerates it when it originates in the cortex, may be important in the further understanding of the special characteristics of the limbic system as compared to the overlying cortical areas.

Our observations concerning the use of artane and similar substances in centrencephalic epilepsy, bear further elaboration and may lead us to a better understanding of the motor phenomena which characterize these seizures.

The psychotic episodes which we have observed as an outward expression of epileptic activity in the temporal lobe are significant because their occurrence demonstrates that epileptic discharge in this region may cuase psychosis. Such a psychosis presents a social, psychiatric, and legal problem and its origin must be clearly understood. It can be reversed and will disappear under effective treatment. When it occurs it resembles some form of adult schizophrenia and may be mistaken for an acute schizophrenic turmoil.

Memory difficulties usually follow temporal lobe seizures which are characterized by deja vu phenomena or by other psychical illusions. This is demonstrated in one case which we outlined above.

Proposed course of the Project: We will continue the clinical studies. With new methods of electrographic recording and stimulation, we must expand our area of observation in the human operating room and on the ward. In the primate laboratory we can now create chronic epileptogenic preparations in the chimpanzee through the use of implantation electrodes which can be controlled (remotely) by radio impulses. In this way we hope to study the behavior of these animals, before, during and after the incidence of these discharges in their temporal lobes, and also analyze the seizure patterns which occur as the result of these discharges. These applied-scientific techniques will be reinforced by observations of a more basic nature which we can accrue from the projects on second sensory areas, somato-sensory localization, and amygdaloid function. All of these projects can be integrated so as to give us a greater knowledge of the phenomena which characterize epileptogenic discharge in the temporal regions. In therapy, we have improved our surgical techniques and we have tested old drugs in new fashions. We hope to devise new surgical techniques and improvise newer pharmocological treatments.

R.P.C. 2
Dec. 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB-46 (C)
SERIAL NO.

11. BUDGET DATA

12. BUDGET ACTIVITY: RESEARCH

13. NONE.

14. NONE.

Honors, Awards, and Publications

16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

17. HONORS AND AWARDS TO PERSONNEL DURING 1955:

None

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
BRANCH

3. Neurosurgical Service
SECTION

4.
LOCATION

5. NINDB-47 (C)
SERIAL NO.

6. Pain Mechanisms
PROJECT TITLE

7. J.M. Van Buren, M.D.
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: A study of patients suffering from painful lesions has been undertaken to provide material for the following studies which will be further elaborated as future evidence indicates: (1) Evaluation of the standard surgical procedures for the relief of pain. (2) Evaluation of standard medical procedures for the relief of pain including some of the newer medications such as stildamidine for the relief of trigeminal neuralgia. (3) Evaluation of objectively recorded autonomic responses by the use of a polygraph in patients with varying degrees of pain. In this study the anticipatory autonomic response to a known and forewarned painful stimulus will be evaluated as well as an attempt made to obtain some quantitative measurement of pain threshhold in patients both free of and suffering from pain. The conjunction of these studies with the above mentioned clinical studies may give more objective evidence to the evaluation of these treatment programs. (4) The section of sensory pathways (pain pathways) affords the opportunity for study of patients with these surgical lesions. The advantage of study in a surgical rather than a neoplastic or diffuse vascular lesion is obvious, in that the lesion is more precise in type and is usually of known dimensions.

Methods Employed: The methods to be used in treatment of pain problems are to include the standard surgical procedures for the relief of pain, either in the peripheral nerve, dorsel root, or central pain pathways. The medical treatment of pain will likewise follow well approved and standard patterns.

PROJECT DESCRIPTION (Continued)

The new feature which will be added to the study of pain is by the use of a polygraph in which blood pressure by an auscultatory method (no arterial puncture) electrocardiogram, respirations, skin resistance, the pressure variations from a plethysmograph and pressure variations in a hollow viscus such as bladder and/or stomach may be recorded. By the simultaneous recording of these data it is hoped that further insight may be gained into the autonomic responses to the painful stimulus in man. At the present time, considerable difficulty in instrumentation is being encountered. Apparently an instrument of this type for simultaneous recording of many modalities has not previously been constructed so that the investigator is undertaking the fabrication and collection of the proper recording instruments. This has delayed progress on the project considerably.

Additional studies of the patient following a central nervous system lesion of known dimension will be undertaken on a clinical level. Problems of interest concern the central pathways for sweating in man which as far as the author is aware have not been elucidated above the upper cervical cord. Another problem of basic nature in which the lesions could be used, is for the study of the pathways of conduction of the muscle spindle afferent impulses.

Patient Material:

		No.	Average Stay - days
Admissions:	Adult Male	4	12.25
	Adult Female	9	36.22
	Children Male	0	
	Children Female	0	

Outpatient:	Number of patients:	15
	Number of visits:	33

Major Findings: Work so far has been directed toward instrumentation.

Significance to Neurological Research: There is preliminary evidence that the autonomic responses to pain and other stimuli in patients suffering pain is enhanced. This will be investigated as possible basis for objective assessment of the individual's response to pain.

Proposed course of the Project: The major hurdle at the present time consists in the proper preparation of the polygraph for autonomic recordings. For this reason the major patient load for this project has been held up.

R.P.C. 2
Dec. 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB- 47 (C)
SERIAL NO.

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11. BUDGET DATA:

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12. BUDGET ACTIVITY: RESEARCH

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13. None

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14. None

Honors, Awards, and Publications

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16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

None

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17. HONORS AND AWARDS TO PERSONNEL DURING 1955:

None

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness — INSTITUTE
2. Surgical Neurology — BRANCH
3. Neurosurgical Service — SECTION
4. ____________ — LOCATION
5. NINDB-48 (C) — SERIAL NO.
6. Special Pathology of Epileptogenic Tissue — PROJECT TITLE
7. Maitland Baldwin, M.D. — PRINCIPAL INVESTIGATOR
8. J.M. Van Buren, M.D. — OTHER INVESTIGATORS
9. PROJECT DESCRIPTION

Objectives: The relationship between epileptic activity and structural change in the brain has been a problem, long basic to the understanding of epilepsy itself. The availability of a considerable quantity of epileptogenic brain tissue removed in operation has formed a unique opportunity for the study of this subject.

Method Employed: The epileptogenic tissue has been divided into two portions. One has been placed for imbedding in parafin. This allows chromatic stains such as the tricrome and phosphotungstic acid hematoxylin stain, reticulin stain and the hematoxylin eosin. The other portion has been set aside in formal-ammonium bromide. This fragmant can be used for metallic stains for the outlining of glia and neurons. Fat and lipid stains can also be carried out on this material. In the future it is hoped to make use of the electron microscope for finer examination of the abnormal cells.

Patient Material:

		No.	Average Stay - days
Admissions:	Adult Male	16	9.12
	Adult Female	21	8.29
	Children Male	6	18.83
	Children Female	5	9.4

Outpatient: Number of patients: -
Number of visits: -

Major Findings: The complete review of the available material has not been finished. Initial findings include the following

PROJECT DESCRIPTION (Continued)

types of lesions: (1) Pseudolaminar necrosis. This lesion is loss of cerebral substance including neurons and glia, limited largely to the central layers of the cerebral cortex. In this area the cerebral substance appears spongy, and is frequently completely destroyed. Lesser changes consist in a loss of neurons in this area. This change is apparently secondary to interference with the fine penetrating blood vessels from the surface of the cerebral cortex. Collateral Golgi stains of cerebral cortex to show the endothelium of the capillaries demonstrates that the maximum density of the capillary network lies in these central layers of the cortex; probably in layer III to upper V. From this, the inference perhaps follows that this area of the cerebral cortex requires the greatest blood supply. It has also been shown by other work that in the lower portion of the cortex a junction is made between the blood supply from the surface and from the white substance. Hence, it is apparent why this area of cerebral cortex is the most vulnerable to mild anoxia. (2) Complete cortical necrosis. This lesion is apparently a continuation of the above-mentioned process in which none of the cerebral cortex remains. (3) Fats and lipid deposition. In many epileptogenic lesions in which there is lack of severe pathological change phagocytes filled with lipid which will stain with sudan IV as well as scharlach have been found in the perivascular spaces and as well at times free in the cerebral substance apparently at a distance from vessels. The origin of this lipid is obscure as in some cases there is no obvious breakdown of myelin in tissue. (4) Neuron damage. Damage to the neurons has appeared in many of the sections. The most common change is that of the dense pyknosis of the cell, shrinkage of the cell in decreasing its lateral dimensions and tortuosity of the apical dendrite. It is considered that in many instances this is a traumatic artifact since there frequently is no surrounding increase in the pericellular satelites. A similar change has been shown in a recent paper by Cecile Vogt, published in the Annals of the First International Congress of Neuropathology. (5) Fibrous astrocytosis of the cortex. In this change, best demonstrated on the metallic impregnations, fibrous astrocytes appear in layers of the cortex in which they are normally absent. They are normally present, of course, in the molecular layer, and occasionally in the VIth layer of the cortex. (6) The meningo-cerebral cicatrix. This is the classical brain scar in which there is a union of the fibrous tissue elements of the dura with the fibrous framework of the cerebral cortex itself, namely the tissue about the blood vessels. There is general hypertrophy of these structures, a fibrillary astrocytosis and loss of fine capillary supply to the affected cerebral cortex. Or, there may be a considerable quantity of debris arising from myelin destruction, and old blood pigment which is deposited in the phagocytes.

R.P.C. 1 (b)
Dec. 1955

NINDB-48 (C)
SERIAL NO.

PROJECT DESCRIPTION (Continued)

Significance to Neurological Research: Although the basis of epilepsy as yet remains obscure, basic studies on the structural changes of epileptic lesions are necessary for an illucidation of its mechanism.

Proposed course of the Project: It is hoped by further study in this direction, particularly with cytochemical methods, that further knowledge of basic importance may be uncovered in this direction.

R.P.C. 2
Dec. 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB-48 (C)
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: RESEARCH

13. None

14. None

Honors, Awards, and Publications

16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

None

17. HONORS AND AWARDS TO PERSONNEL DURING 1955:

None

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
BRANCH

3. Neurosurgical Service
SECTION

4. ______________
LOCATION

5. NINDB-49 (C)
SERIAL NO.

6. Effect of Tumors upon Central Nervous System Function and Structure.
PROJECT TITLE

7. J.M. Van Buren, M.D.
PRINCIPAL INVESTIGATOR

8. M. Baldwin, M.D. and Philip Rubin, M.D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: This study has a dual aim: 1) to carry out physiological-anatomical correlations in man, 2) to evaluate the effects of newer methods of treatment for tumors of the central nervous system. In the present program attempt will be made to utilize the intrusion of disease upon the central nervous system of man as an "experimental" lesion.

Although much can be accomplished through animal experimentation in determining the function of structures within the nervous system it is apparent that the need for confirmation of these findings in man is ever present. In addition, studies of function which cannot be properly evaluated in animals (e.g., sweating) must be carried out in man. Although the fruits of a study of this type are of widespread nature, particular attention has been placed upon three major features: (1) To note the effects of neoplasm upon the function of the optic pathways of man and particularly upon the correlation of the visual fields and the anatomical changes in retina, geniculate body and calcarine cortex. (2) To study, particularly in cases of slowly expanding lesions of the upper brain stem, the effects of these lesions upon personality, consciousness and the electroencephalogram. Since the majority of these lesions are of terminal nature, opportunity therefore will arise for clinical-anatomical correlation.

PROJECT DESCRIPTION (Continued)

Methods Employed: The evaluation on a clinical basis of the position and nature of the tumor will be determined as can best be done by history, neurological examination, contrast examinations, and surgery.. The symptoms under consideration will be evaluated using largely clinical methods, although it is hoped that the polygraph needed for autonomic evaluation will be of aid in this direction. In the post-mortem examination, careful serial examination of the involved structures will be undertaken both grossly and microscopically and charts prepared from this material. By the use of these charts and the method of overlapping areas it is hoped that features of localizing anatomical significance may be discovered.

Patient Material:

		No.	Average Stay - days
Admissions:	Adult Male	17	24.88
	Adult Female	15	19.07
	Children Male	1	19.0
	Children Female	4	37.25

Outpatient: Number of patients: 12
Number of visits: 33

Major Findings: With regard to the visual field pathways in man, it has been found that a lesion affecting the pre-geniculate pathways will cause degeneration in the retina supplied by these fibers which is obvious on microscopic examination. In cases in which there has been partial loss of ganglion cells within the retina it is possible to correlate visual acuity and visual field with two-dimensional reconstructions of the retina. At the present time data regarding the effects of brain tumors upon the level of consciousness, personality and EEG are too few for evaluation. It is too early to evaluate the results of therapy.

Significance to Neurological Research: Neurophysiological data in animals is extensive but research of this type if it is to be helpful in the evaluation or treatment of human disease must be confirmed in man. Since critical evaluation of vision, personality and consciousness cannot be made in animals and the human EEG is species specific in type, re-evaluation of these phenomena in man is necessary. The new surgical-radiotherapeutic techniques have not as yet been carefully investigated in any considerable series of tumors of the central nervous system.

Proposed course of the Project: The accumulation of a large number of cases for a study of this type in which overlapping areas of involvement must be charted is imperative before results of any reliability can be achieved. Thus our present problem is one of collection of data.

R.P.C. 2
Dec. 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB-49 (C)
SERIAL NO.

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11. BUDGET DATA:

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12. BUDGET ACTIVITY: RESEARCH

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13. None

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14. None

Honors, Awards, and Publications

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16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

None

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17. HONORS AND AWARDS TO PERSONNEL DURING 1955:

None

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
BRANCH

3. Neurosurgical Service
SECTION

4. ____________
LOCATION

5. NINDB-50 (C)
SERIAL NO.

6. The Pneumographic Effects of Non-Expanding Epileptogenic Lesions of the Temporal Lobe.
PROJECT TITLE

7. J.M. Van Buren, M.D.
PRINCIPAL INVESTIGATOR

8. Maitland Baldwin, M.D. and E. Alvord, M.D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: This study has been undertaken to elucidate the effects of atrophic lesions upon the outlines of the temporal horn. There have been no previous studies of the lateralizing and localizing value of minor changes and the configuration of the temporal horn in epilepsy.

Methods Employed: The anatomy of structures outlining the temporal horn were reviewed in the embryo and in normal adult human brains. The variations of normal were reviewed in this connection. In 41 cases of proven epilepsy in the temporal lobe the pneumographic evidence was reviewed and the temporal horns measured in a systematic manner.

Patient Material:

		No.	Average Stay - days
Admissions:	Adult Male	18	-
	Adult Female	23	-
	Children Male	-	
	Children Female	-	

Outpatient: Number of patients: 0
Number of visits: 0

PROJECT DESCRIPTION (Continued)

Major Findings: It became apparent that the features outlining the temporal horn consisted of the amygdala, the hippocampus, the roof of the temporal horn (formed largely by the tapetum), and the collateral emminence. Depending on the position of the collateral emminence, four types of normal temporal horns can be distinguished on the sagittal views of the temporal horn. In addition, instances were found in which adhesions had occurred between the lateral border of the hippocampus and the lateral wall of the temporal horn. This might be a cause for lack of filling of the lateral cleft. This defect was not recognized, however, in the clinical material.

After carefully considering the problem, it appears that we were in no position to determine the limits of normality in any of the measurements of the temporal horn. Consequently, the evidence as obtained from history, physical examination, electroencephelography and the findings at craniotomy, including electrocorticography were taken as the absolute criteria for lateralization of the epileptic discharge in the temporal lobe. Arbitrary criteria were then applied to all of the measurements of the temporal horn. These arbitrary criteria were varied to obtain the maximum degree of agreement between the findings of what was considered abnormality on this basis and the actual lateralization of discharge within the temporal lobe. The criteria finally arrived at as indicating enlargement and therefore significant atrophy within the temporal lobe were (1) over 3 mm. greater height of the temporal horn on the affected side, or (2) over 4 mm. in width of the lateral cleft on the affected side. In cases in which the lateral cleft on both sides was greater than 4 mm. the larger one was selected as showing abnormality. Using these criteria alone, of the 28 cases considered to show sufficient filling of the temporal horns for evaluation, 12 showed no asymmetry, 13 showed evidence of dilatation of the temporal horn on the side from whence the epilepsy arose, while 3, on the basis of this criteria, were lateralized to the wrong side.

Significance to Neurological Research: It had been felt that of the criteria used for lateralization and localization of epileptic discharge in seizure discharge from the temporal region, that the pneumoencephalogram usually provided the least information. On the basis of this present study, and better criteria for evaluation of abnormality in the temporal horn, it has been found that in cases with adequate filling nearly 50% show some degree of enlargement of the temporal horn of sufficient degree to suggest lateralization from the pneumographic evidence alone.

Proposed course of the Project: This project has been finished and the report is in press with Acta Radiologica.

R.P.C. 2
Dec. 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB-50 (C)
SERIAL NO.

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11. BUDGET DATA:

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12. BUDGET ACTIVITY: RESEARCH

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13. None

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14. None

Honors, Awards, and Publications

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16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

1) The temporal horn, its development, normal variations and changes with non-expanding epileptogenic lesions of the temporal lobe. Acta Radiologica (in press).

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17. HONORS AND AWARDS TO PERSONNEL DURING 1955:

None

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
BRANCH

3. Neurosurgical Service
SECTION

4. ____________
LOCATION

5. NINDB - 51 (C)
SERIAL NO.

6. A Histological Study of Papilledema using the Golgi Method in Man.
PROJECT TITLE

7. J.M. Van Buren, M.D.
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective: It is the object of this work to further advance knowledge as to the precise changes occurring in the eye in papilledema. Although sporadic papers regarding the cytopathology of papilledema have appeared in the past 50 years, in only one instances (Cone and MacMillan) have attempts been made by the use of specific metallic methods to stain completely the structures undergoing change of papilledema. As far as is known to the author no studies with the Golgi method have been made previously in adult human autopsy material.

Method Employed: It is of primary importance to fix the retina immediately following death. In order to accomplish this, concentrated formalin is injected within the globe at the bedside. By the time the post-mortem examination is undertaken, the retina has been completely fixed and the posterior part of the eye can be removed without damaging the retina. Fixation is then continued in 10% formalin until it is convenient to undertake the Golgi staining. The staining method is a combination of potassium bichromate and potassium acetate mixture in which the eye is incubated at 37 degrees for 10 days to 2 weeks. It is then transferred to a warm 1% silver nitrate solution for 48 hours. The eyes are then rapidly dehydrated in absolute alcohol and transferred immediately to thin celloidin in which they are kept for 48 hours. Following this they are transferred to thick celloidin for a few minutes, then transferred to a mounting block, thick celloidin poured over the specimen, and the whole specimen and the mounting block immediately immersed in chloroform for hardening. Thus the eyes are not infiltrated but rather included in the celloidin. This inclusion is sufficient to permit sectioning at 100 micron intervals which is needed for this method.

PROJECT DESCRIPTION (Continued)

Patient Material:

		No.	Average Stay - days
Admissions:	Adult Male	2	-
	Adult Female	1	-
	Children Male	0	
	Children Female	0	
Outpatient:	Number of patients:	0	
	Number of visits:	0	

Major Findings: To date, the following has been apparent: There are definite, well defined grape-like swellings upon the optic nerve fibers in the optic papilla. These in all instances have appeared on the retinal side of the lamina cribrosa. A careful study of the fiber structure of the lamina cribrosa itself has been undertaken and indications are that in addition to bending away from the cavity of the eye with papilledema that there is also a separation of lamina cribrosa from the margin of Bruch's membrane. The nerve fibers have also been stained at the margin of Bruch's membrane, and their confinement by the sharp edge of this membrane is apparent. They make a very sharp detour around this edge, and it is not difficult to see how they might be injured by the increased pressure on this sharp margin.

Significance to Neurological Research: The sharp angulation of the peripheral retinal fibers over the margin of Bruch's membrane may possibly find its clinical counterpart in the constriction of the paripheral portions of the visual field. Further study must be undertaken on this subject. The precise cause and structural concomitants of papilledema have not been elucidated to date in the literature.

Proposed course of the Project: At the present time the eyes from only three patients have proved suitable for study. More material is needed before detailed results can be advanced.

R.P.C. 2
Dec. 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB-51 (C)
SERIAL NO.

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11. BUDGET DATA:

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12. BUDGET ACTIVITY: RESEARCH

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13. None

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14. None

Honors, Awards, and Publications

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16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

None

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17. HONORS AND AWARDS TO PERSONNEL DURING 1955:

None

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
BRANCH

3. Neurosurgical Service
SECTION

4. ____________
LOCATION

5. NINDB-52 (C)
SERIAL NO.

6. The Histological Investigation of a Case of Retinal Moniliasis.
PROJECT TITLE

7. J. M. Van Buren, M.D.
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective: The chance finding of a case of retinal moniliasis and the availability of the retina for detailed examination has prompted a thorough study of the histological features. As far as is known, no previous case of monilia infection of the retina has been recorded.

Method Employed: The eyes were obtained at post-mortem some 5 hours following death. They are fixed in formalin, imbedded in parafin, and then serially sectioned by the investigator so that the small monilia lesion would not be overlooked. Routine histological stains were carried out including the PAS which demonstrated the monilia hyphae within the granulation tissue.

Patient Material:

		No.	Average Stay - days
Admissions:	Adult Male	-	-
	Adult Female	1	-
	Children Male	-	
	Children Female	-	
Outpatient:	Number of patients:	-	
	Number of visits:	-	

Major Findings: The lesion in the retina was thought to have had its origin just below the internal limiting membrane, presumably being an embolic infection which had lodged in a small vessel. It had depressed the subjacent retina, considerably thinning out the ganglian cell layer and the internal molecular layer. Exudate had broken through the internal limiting membrane and had spread in the subhyaloid space. Indeed, leucocytes were present over the papilla some distance from the initial infection.

R.P.C. 1 (a)
Dec. 1955

NINDB-52 (C)
SERIAL NO.

PROJECT DESCRIPTION (Continued)

Significance to Neurological Research: Although the case is an isolated one, the fact that it is apparently new to the ophthalmological literature suggested that it was worthy of review and report.

Proposed course of the Project: Additional histological work remains to be done, literature review must be continued and the report written in final form.

R.P.C. 2
Dec. 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB-52 (C)
SERIAL NO.

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11. BUDGET DATA:

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12. BUDGET ACTIVITY: RESEARCH

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13. None

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14. None

Honors, Awards, and Publications

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16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

None

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17. HONORS AND AWARDS TO PERSONNEL DURING 1955:

None

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
BRANCH

3. Neurosurgical Service
SECTION

4. ______
LOCATION

5. NINDB-53 (C)
SERIAL NO.

6. Study of the Adult Human Retinal Cytology using Golgi and Chromatic Methods.
PROJECT TITLE

7. J.M. Van Buren, M.D.
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective: This study of normal retinal cytology is undertaken as a basis for the evaluation of degenerative lesions in the retina. As far as can be determined, no previous work has been carried out using the Golgi method in the adult human retina. A considerable portion of the available reports of retinal cytology are confused by post-mortem artifact. By the use of early retinal fixation these artifacts may be eliminated.

Method Employed: The study will be carried with human retinas fixed within half an hour of death by intra-ocular injection of formalin. Some will be stained by the Golgi and others by chromatic methods.

The Golgi method will be used primarily for study of the conformation of individual retinal elements, while the chromatic methods will be used primarily for the study of retinal cyto-architecture. In the latter connection, serial sections will be made of the eyes, and from these, 2 dimensional reconstructions of the retina and its various cell fields can be made.

Patient Material:

		No.	Average Stay - days
Admissions:	Adult Male	2	-
	Adult Female	2	-
	Children Male	-	
	Children Female	-	

Outpatient: Number of patients: -
Number of visits: -

R.P.C. 1 (a)
Dec. 1955

NINDB-53 (C)
SERIAL NO.

PROJECT DESCRIPTION (Continued)

Major Findings: To date, perhaps the most important finding has been that human post-mortem material has proved suitable for Golgi staining. As far as is known, a Golgi method suitable for routine post-mortem work has not been previously employed. At the present time, the nature of various components of the retina is being investigated by this means.

Using the chromatic method, variations in the types of ganglion cells have been found from the central fovea to the periphery, and the varying thickness of the ganglion cell layer as described by other investigators has been confirmed. At the present time, only four retinas serially sectioned have been obtained in which visual fields were done prior to death. The correlation between this retinal degeneration and the visual field is of primary importance. It is planned to convert retinal distances as measured off in the various cell fields into visual angle. From this, a simultaneous charting of the retinal cell fields and the visual fields as determined clinically can be carried out. It is hoped that this anatomical-clinical comparison may prove fruitful.

One interesting variant has been found on the chromatic stains which consists in the not infrequent displacement of ganglion cells and other retinal elements outside of their commonly accepted zones.

Significance to Neurological Research: Although Golgi studies of retinae in low animals has been carried out, it seems desirable to confirm the cytological findings in man. Such an opportunity now presents itself.

A further study in the normal variants in the human retina is necessary to determine the limits of normal.

The correlation between the anatomical configuration of the retina and the visual field is obviously of basic importance to the proper evaluation of visual field studies.

Proposed course of the Project: More human autopsy material is desirable. The methods as devised above have proved satisfactory and must be applied to more cases. Further reconstructions must be made in cases of serially sectioned retinae presently available.

R.P.C. 2
Dec. 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB-53 (C)
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: RESEARCH

13. None

14. None

Honors, Awards, and Publications

16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

None

17. HONORS AND AWARDS TO PERSONNEL DURING 1955:

None

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
BRANCH

3. Neurosurgical Service
SECTION

4. ____________
LOCATION

5. NINDB-54 (C)
SERIAL NO.

6. The Effect of Lesions of the Optic Pathways upon the Retina.
PROJECT TITLE

7. J.M. Van Buren, M.D.
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective: Study will be made of the effects of degeneration upon the areal pattern of ganglion cells in the retina by the use of reconstruction technique. Attention will also be paid to other retinal layers to determine the degree of transynoptic and transneuronal degeneration. As far as the author is aware, only one case of retinal degeneration following a lesion of the pregeniculate pathway has been reported in man. In no instances have retinal changes from postgeniculate changes been recorded in man, although Polyak has recorded one instance to the author's knowledge in a monkey. Human material is presently available for evaluation, and lesions have been placed in macaques some 12 months ago, which are presently ready for study.

Method Employed: The eyes were fixed by intra-ocular injection of formalin, marked for orientation on the slide, imbedded in paraffin and serially sectioned. Degenerated areas were marked out with ink on the slides, the slides projected at 35x magnification and traced upon paper. The degenerated areas on the tracing were measured, then from these measurements a two-dimensional reconstruction made. Conversion of retinal distances to degrees of visual angle permitted the superimposition of the areas of degeneration upon the clinically recorded visual field.

Patient Material:

		No.	Average Stay - days
Admissions:	Adult Male	1	10
	Adult Female	-	
	Children Male	-	
	Children Female	-	

Outpatient: Number of patients: -
Number of visits: -

PROJECT DESCRIPTION (Continued)

Major Findings: In both monkeys and a human case it has been found that lesions of the pre-geniculate optic path are followed by a definite degeneration in the retina. If, indeed, complete section of an optic tract is carried out, this degeneration will encrouch upon one-half of the fovea and extend above and below this foveal point in a vertical straight line. By the use of reconstruction studies in the human case, the conversion of retinal distances into visual angles, and the simultaneous charting of degenerative areas in the visual field, it has been possible to compare the anatomical with the clinically determined findings. In like fashion, it has been possible to compare the visual acuity with the degree of retinal degeneration.

Significance to Neurological Research: These studies of purely destructive regions of the geniculate optic pathway are intended to elucidate the pathological changes in the retina following such a lesion. A clinical anatomical correlation is believed of basic importance for the understanding of the significance of visual field studies.

Proposed course of the Project: Although there is no lack of animal material, every possible advantage will be made of additional human material as it presents itself. It is felt that the major emphasis must be upon human material as this is an unexplored field.

Analysis of NIH Program Activities

Budget Data

10. NINDB-54 (C)
SERIAL NO.

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11. BUDGET DATA:

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12. BUDGET ACTIVITY: RESEARCH

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13. None

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14. None

Honors, Awards, and Publications

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16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

None

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17. HONORS AND AWARDS TO PERSONNEL DURING 1955:

None

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
BRANCH

3. Neurosurgical Service
SECTION

4.
LOCATION

5. NINDB-55 (C)
SERIAL NO.

6. The Effect of Lesions of the Optic Pathways upon the Geniculate Body.
PROJECT TITLE

7. J.M. Van Buren, M.D.
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objective: Since the visual field changes following temporal lobectomy have been carefully observed in another study of this series, it has been thought of interest to study the geniculate representation of this visual field change. As far as the author is aware, no previous studies of the geniculate body following temporal lobectomy in man have been carried out.

Method Employed: The brains from two patients in which the temporal lobes were removed were fixed in 10% formalin, the slices containing the geniculate bodies separated, imbedded in celloidin and serially sectioned, keeping sections at 500 micron intervals. The sections were stained for Nissl substance and myelin. The sections were then photographed at 50 x magnification, and the entire geniculate body printed at this size. The degenerative lesion, therefore, could be made out on the photographic prints and its precise dimensions and details made out by simultaneous comparison under microscope. By this means, the layering and the lesion could be outlined with pencil, subsequently drawn over in india ink, and then rephotographed to diminish the size to a degree that would permit publication. If it is desired later for demonstration purposes, 3 dimensional model can be made.

Patient Material:

		No.	Average Stay - days
Admissions:	Adult Male	2	-
	Adult Female	-	
	Children Male	-	
	Children Female	-	
Outpatient:	Number of patients:	-	
	Number of visits:	-	

PROJECT DESCRIPTION (Continued)

Major Findings: It has become apparent that following temporal lobe lesions, degeneration does not extend to all six layers of the geniculate body, as has been postulated with lesions in the occipital lobe. Since the visual field changes do not affect the macular portion of the visual field, it gives some suggestion that the macular representation may lie somewhat deeper within the geniculate body than the portions subserving upper quadrantic gaze which are destroyed in temporal lobectomy.

Significance to Neurological Research: This study is intended as a further approach to clinical-anatomical correlation of visual function in man.

Proposed course of the Project: The above conclusions were reached on a study of one case only. The other case remains to be charted and reconstructed. It is hoped that it will be possible to obtain a third case for confirmation. Later on, when some chimpanzees with temporal ablations are autopsied, further confirmation of the degeneration in the anthropoid ape will be obtained.

R.P.C. 2
Dec. 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB - 55 (C)
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: RESEARCH

13. None

14. None

Honors, Awards, and Publications

16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

None

17. HONORS AND AWARDS TO PERSONNEL DURING 1955:

None

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
BRANCH

3. Experimental Neurosurgery
SECTION

4. ____
LOCATION

5. NINDB-56 (C)
SERIAL NO.

6. Microelectrode Studies of the Cerebral Cortex in Experimental Animals and Man.

7. Choh-luh Li, M. D.

8. Maitland Baldwin, M. D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Project: Development of methods for recording electrode activity of single cells from the human and animal cortex.

Objectives: To develop methods which can be adapted in the human operating room for the recording of electrical activity of single cortical cells, particularly in epileptic patients, with the purpose of studying the mechanism of epilepsy.

To apply these methods to the human cortex and to the cortex of experimental animals. After this application to test the effects of stimulation of the deep-lying nuclei on single unit activity in the cortex to which these methods were applied.

Methods Employed: Microelectrodes made of glass capillary pipettes with an inside diameter of less than half a micron are used for recording electrical activity from single cells.

This microelectrode technique was applied with a number of variations. The effect of strychninization was studied in experimental animals and the effect of recruiting responses was also observed. Likewise, this technique was so adapted that it might be used to study the action of resting potentials of cortical neurones.

Major Findings: The major findings of this project during the past year are:

(a) Recording of single unit potential activity from the human cortex in two cases and from the chimpanzee cortex in two of these experimental animals. Furthermore, we have studied the functional properties of cortical neurones with particular reference to strychninization, as well as the effect of recruiting responses of evoked neuronal discharge in experimental animals.

(b) More recently, we have studied the action and resting potentials of these single cortical units and observed the facilitatory effect of stimulation of unspecific thalamic nuclei on cortical sensory neuronal responses, and finally, the inhibitory effect on cortical moto-

Major Findings (continued)
neuronal activity of stimulation of thalamic nuclei on single motor units in the cortex of experimental animals. We have also observed that single units in the motor cortex are inhibited after deep stimulation of certain thalamic nuclei.

Significance to Research: The study of single unit potentials and the characteristics of single neuronal units in the higher primate nervous system has great significance to the better understanding of function. The single cortical unit is basic in the relationships of the various cortical areas and its individual characteristics have not been studied. Furthermore, these individual characteristics as observed in the normal human and experimental animals may lead us to further conclusions concerning the activity of such neurones under the abnormal conditions of the epileptogenic cortical lesion.

Proposed Course: During the next year we will study the effects produced in single cortical units following deep stimulation of thalamic and other nuclei. We will also study the human epileptogenic cortex with the microelectrode techniques and we will study normal and epileptic preparations in man and the higher primates.

R.P.C. 2
Dec. 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB-56 (C)
SERIAL NO.

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11. BUDGET DATA

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12. BUDGET ACTIVITY: RESEARCH

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13. NONE

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14. NONE

Honors, Awards, and Publications

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16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

Functional properties of cortical neurones with particular reference to strychninization. J. EEG Clin. Neurophysiol., 1955. 7:475-478.

The effect of recruiting responses on evoked cortical neuronal discharges. East-Southern EEG Society Meeting, Sept. 1955, Bethesda, Md.

Action and resting potentials of cortical neurones, J. Physiol., Vol. 130, 1955, 96-108.

The facilitatory effect of stimulation of an unspecific thalamic nucleus on cortical sensory neuronal responses. J. Physiol. (in press).

The inhibitory effect of stimulation of thalamic nuclei on cortical motoneuronal activity (manuscript in preparation).

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17. HONORS AND AWARDS TO PERSONNEL DURING 1955:

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
BRANCH

3. Clinical Neuropathology
SECTION

4. ____________
LOCATION

5. NINDB-57 (C)
SERIAL NO.

6. Relation of Supraspinal Structures to an Experimental Startle Reaction
PROJECT TITLE

7. Ellsworth C. Alvord, Jr., M.D.
PRINCIPAL INVESTIGATOR

8. David G. Whitlock, M.D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To determine the neuroanatomical and physiological substrata of the startle reaction.

Methods Employed: Acute and chronic lesions of the central nervous system of cats have been made in various locations to determine the effects of such lesions upon the generalized muscular contractions which can be reflexly evoked by various suddenly applied stimuli in cats under chloralose anesthesia. Other experiments have been performed utilizing a stereotaxically oriented electrode to explore the C.N.S., both by recording evoked electrical potential from and by applying single electrical stimuli to localized regions of the C.N.S.

Major Findings: In brief, it has been found that the sensory motor area of the cerebral cortex influences the sensitivity of the animals to the startle reflex while under light chloralose anesthesia. This was tested by removal of the sensory motor area. Then while under chloralose anesthesia, the testing of the response to tactile stimuli were carried out a week later. It was found that the threshold was raised on the portion of the body corresponding to the area of decortication.

Significance to Neurological Research: Study of the startle reaction provides basic information concerning the organization of the nervous system, particularly with respect to its more diffusely organized functions, and is of importance in the understanding of reflex activity in general and perhaps of reflexly induced epileptic seizures in experimental animals and patients. Since chloralose is frequently used in neurophysiological experiments, further knowledge of its actions is also important.

PROJECT DESCRIPTION (Continued)

Proposed course of the Project: At the present time, the paper is being prepared by the investigators for publication. Dr. Alvord has transferred his work to Baylor University.

R.P.C. 2
Dec. 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB-57 (C)
SERIAL NO.

12. ______________________________
BUDGET ACTIVITY: RESEARCH

Honors, Awards and Publications

16. ______________________________
PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING 1955:

None

17. ______________________________
HONORS AND AWARDS TO PERSONNEL DURING 1955:

None

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
BRANCH

3. Clinical Neuropathology
SECTION

4. ____________
LOCATION

5. NINDB- 58 (C)
SERIAL NO.

6. Pathogenesis of "Allergic Encephalomyelitis"
PROJECT TITLE

7. Ellsworth C. Alvord, Jr., M.D.
PRINCIPAL INVESTIGATOR

8. Norman Goldstein
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To determine the cause and the mechanism underlying the development of disseminated encephalomyelitis.

Methods Employed: Brain and various extracts of brain are prepared in a water and oil emulsion with killed acid-fast bacilli. Following subcutaneous inoculation into guinea pigs, the animals are examined for clinical evidence of weakness, incoordination, or other neurological disorder. The spinal cord and brain are examined histologically for presence of characteristic perivascular inflammation sometimes with demyelinization.

Major Findings: A total of 450 animals have been studied. 50 animals were killed two days following the injection of the brain and brain extract material in order to study the early lesions. The remaining 400 animals served as control and were injected with different brain fractions and sacrificed at the end of the 30 day period. The earliest lesions which were seen on the second day consisted in perivascular inflammatory response usually in the lower brain stem and spinal cord. The incidence of inflammatory lesions rose considerably after this time as was expected. At the present time the experimental work has been completed.

Significance to Neurological Research: Study of the etiology and pathogenesis of "allergic" encephalomyelitis in experimental animals will yield information of importance to patients treated with vaccines containing brain material, as in anti-rabies inoculations, and may also yield pertinent information on diseases which appear histologically quite similar and may be related, as in other post-vaccinal and post-infectious encephalomyelitis. Its relation to multiple sclerosis and other demyelinating diseases remains to be determined.

PROJECT DESCRIPTION (Continued)

Proposed course of the Project: The findings in the cases of early allergic encephalomyelitic lesions are being correlated by Dr. Kenneth McGee for publication. The results in the other 400 animals used to evaluate the effectiveness of various chemical fractions of the brain in producing allergic encephalomyelitis is being reviewed by Dr. Kies at NIMH and Dr. Alvord at Baylor University.

R.P.C. 2
Dec. 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB - 58 (C)
SERIAL NO.

12.
BUDGET ACTIVITY: RESEARCH

Honors, Awards, and Publications

16.
PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING 1955:

None

17.
HONORS AND AWARDS TO PERSONNEL DURING 1955:

None

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
BRANCH

3. Clinical Neuropathology
SECTION

4. ________
LOCATION

5. NINDB-59 (C)
SERIAL NO.

6. Neuropathologic Investigation of Focal Epilepsy and other Neurological Diseases
PROJECT TITLE

7. Ellsworth C. Alvord, Jr., M.D.
PRINCIPAL INVESTIGATOR

8. Dr. Brace
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: Experiments have been performed to determine the effects of high doses of X-irradiation on the nervous system of guinea pigs.

Major Findings: 50 animals have been received for histopathologic study with particular emphasis on changes in the cerebellar granule cells. Interest centers especially about the time course of these changes, their variation with different doses of X-ray delivered to different parts of the head and body, and their modification by drugs such as nembutal.

Significance to Neurological Research: The experiments in animals provide an opportunity to analize the means by which the brain reacts to various injurious agents such as X-radiation, which are being used in increasing dosage for therapy in human neoplastic disease.

Proposed course of the Project: This paper has been finished and was presented at the Second International Neuropathological Congress in London under the title of "X-Ray Induced Pyknosis of Cerebellar Branule Cells in Guinea Pigs." It was also submitted to the Journal of Neuropathology and Experimental Neurology.

R.P.C. 2
Dec. 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB - 59 (C)
SERIAL NO.

12. ______________________________
BUDGET ACTIVITY: RESEARCH

Honors, Awards, and Publications

16. ______________________________
PUBLICATIONS FROM THIS PROJECT DURING 1955:

1) X-Ray Induced Pyknosis of Cerebellar Granule Cells in Guinea Pigs. Submitted to the Journal of Neuropathology and Experimental Neurology.

17. ______________________________
HONORS AND AWARDS TO PERSONNEL DURING 1955:

None

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
BRANCH

3. Clinical Neuropathology
SECTION

4. ________
LOCATION

5. NINDB-60 (C)
SERIAL NO.

6. Neuropathologic Investigation of Focal Epilepsy and Neurological Diseases
PROJECT TITLE

7. Ellsworth C. Alvord, Jr., M.D.
PRINCIPAL INVESTIGATOR

8. John Lilly
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objective: To determine the relative degree of damage to the cerebral cortex by repetitive electrical stimulation with different wave forms of electrical current.

Major Findings: One monkey after 7 weeks of daily prolonged stimulation by electrical currents of special wave characteristics showed moderate gliosis of the cortex with good preservation of the neurons. Other animals are now being prepared in attempt to control the effects of operative trauma and of stimulation by different electrical wave forms to test the hypothesis that repetitive electrical stimulation need not necessarily destroy the neurons.

Course of the Project: Studies are being presently continued by Dr. Lilly.

R.P.C. 2
Dec. 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB - 60 (C)
SERIAL NO.

11. BUDGET DATA

12. BUDGET ACTIVITY: RESEARCH

13. NONE

14. NONE

HONORS, AWARDS AND PUBLICATIONS

16. PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING 1955:

17. HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

R.P.C. 1
December 1955 Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
LABORATORY OR BRANCH

3. Clinical Psychology
SECTION

4.
LOCATION (OTHER THAN BETHESDA)

5. NINDB-61 (C)
SERIAL NO.

6. Functioning of the Temporal Lobe in the Recording of Experiences.
PROJECT TITLE

7. Laurence L. Frost
PRINCIPAL INVESTIGATOR

8. Maitland Baldwin, Mildred Blevins
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

OBJECTIVES: To determine the role of the temporal lobe with its structures and central connections, in learning, recollection, recall, and reproduction.

METHODS EMPLOYED:
a. Psychological tests and specific measures of learning administered to patients with temporal lobe seizures prior to and following removal of one or the other temporal lobe. These same tests administered to patients with bilateral temporal lobe damage and to patients with damage in cerebral areas other than the temporal lobe.
b. Observation of and tests on monkeys and chimpanzees subjected to bilateral temporal lobe removal.
c. Observation of imitative learning and general retentiveness in infant monkeys who have had both temporal lobes removed.

PATIENT MATERIAL:

		No.	Average Stay - days
Inpatient:	Adult Male	14	47
	Adult Female	10	46
	Child Male	2	49
	Child Female	3	45
Outpatient:	Number of patients:	10	
	Number of visits:	15	

MAJOR FINDINGS:
a. Psychological tests indicate that memory, so commonly defined, is not altered or rendered non-functional by the presence or removal of a damaged temporal lobe. What seems more likely is that functions of attention and concentration are changed in such a manner that the patients attention fluctuates rapidly and that it is difficult for him to maintain a state of concentration. A test devised to measure the recording and comparing of experiences indicates that many patients with cerebral pathology, cortical or sub-cortical, have difficulty in so doing when compared with a "normal" group.

b. Observation of monkeys and chimpanzees following unilateral and bilateral temporal removals reveals nothing in the way of decreased ability to record prior experiences. Rare "oral" tendencies as reported by Klüver and Bucy have been transient; Some alteration in the recognition of "textures" may be present.
c. Infant monkeys have had their temporal lobes removed bilaterally. When reestablished in the general monkey colony, no differences were noted between them and their fellows. They learned and imitated readily. There was no outstanding "tameness."

SIGNIFICANCE TO THE PROGRAM OF THE INSTITUTE: Epileptic patients in general frequently complain of a memory loss, and temporal lobe patients in particular occasionally have a "memory" aura; as well, "memory" responses are occasionally obtained during stimulation at operation. This project hopes to be able to define memory and to learn the part played in the recording of experiences by the temporal lobe; as such it is related to the project: Mechanism of Memory, Branch of Surgical Neurology.

PROPOSED COURSE OF PROJECT: Continue the present line of research with greater emphasis placed on bitemporal lesions, and lesions of other than temporal areas.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-61 (C)
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: RESEARCH

13. NONE

14. NONE

Honors, Awards, and Publications

15.
SERIAL NO.

16. PUBLICATIONS OTHER THAN THIS PROJECT DURING 1955.

NONE

17. HONORS AND AWARDS TO PERSONNEL DURING 1955.

NONE

R.P.C. 1
December 1955 Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
LABORATORY OR BRANCH

3. Clinical Psychology
SECTION

4.
LOCATION (OTHER THAN BETHESDA)

5. NINDB-62 (C)
SERIAL NO.

6. The Role of the Temporal Lobe in Perception.
PROJECT TITLE

7. Laurence L. Frost
PRINCIPAL INVESTIGATOR

8. Mildred Blevins, Maitland Baldwin
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

OBJECTIVES: An attempt to determine the role of the temporal lobe in the perception of visual, auditory, and tactual stimuli.

METHODS EMPLOYED:
a. Standard psychological and neurological tests of perception administered to patients with temporal lobe electrographic foci. The same tests administered to patients with electrographic foci elsewhere in the cerebral hemispheres, or diffuse electrographic disturbances, and to patients and controls who have no abnormal cerebral findings.
b. Two tests devised, one primarily for perception, one primarily for learning.
c. Conditional discriminations with primates and electrical stimulation of the temporal lobe and its hypothecated connections.

PATIENT MATERIAL:

		No.	Average Stay - days
In patient:	Adult Male	20	46
	Adult Female	22	45
	Child Male	8	48
	Child Female	9	45
Outpatient:	Number of patients	15	
	Number of visits	22	

MAJOR FINDINGS:
a. Perception as measured by standard psychological and neurological tests indicates that cerebral injury, focal or diffuse, precludes accurate perception. The more gross the injury the more unclear the perception. It is becoming apparent that temporal lobe foci tend to alter in a subtle manner the perception of relationships to other individuals. This is different in crucial ways from perception and relationship problems faced by others with cerebral and sub-cortical injury.
b. The special test devised for perception indicates that some

patients with focal cortical injury may show an initial facility for more fluid perception which becomes increasingly rigid in the patient is found to make more broad interpretations of his perceptions. This data does not seem true of those with diffuse cerebral damage or those with apparently normal cerebral function.

The test devised primarily for learning indicates that auditory perception of those with cerebral damage may be altered, particularly in the recognition of auditory stimulii.

c. Stimulation of an hypothecated connection between the primate temporal lobes (the anterior commissure) apparently grossly altered the monkey's perception of his environment for the duration of the stimulation. This same result has been seen on occasion following stimulation of the depths of one temporal lobe.

SIGNIFICANCE TO THE PROGRAM OF THE INSTITUTE: Perception and its interpretation plays a major role in personality. Since perception is seemingly altered in a subtle manner in patients with temporal lobe damage. The definition of this alteration is basic to the understanding of the temporal lobe. As well this project is allied to projects titled: Mechanism of Memory and Visual Field. Defects following Temporal Lobectomy. These latter two projects are directly from the Branch of Surgical Neurology.

PROPOSED COURSE OF PROJECT: Continuation of the present lines of inquiry, modified as further investigation dictates. It will be necessary to gather information on perception from a greater number of patients with focal electrographic changes elsewhere in the cerebral cortex and sub-cortical structures.

Budget Data Sheet

10. NINDB-62 (C)
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: RESEARCH

13. NONE

14. NONE

Honors, Awards, and Publications Sheet

15. ____________
SERIAL NO.

16. PUBLICATIONS OTHER THAN THIS PROJECT DURING 1955.

NONE

17. HONORS AND AWARDS TO PERSONNEL DURING 1955.

NONE

R.P.C. 1
December 1955 Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
LABORATORY OR BRANCH

3. Clinical Psychology
SECTION

4.
LOCATION (OTHER THAN BETHESDA)

5. NINDB-63 (C)
SERIAL NO.

6. Speech Areas in Man
PROJECT TITLE

7. Laurence L. Frost
PRINCIPAL INVESTIGATOR

8. Maitland Baldwin
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

OBJECTIVES: Localization of brain areas involved in the production and interpretation of speech. Determination of types of speech errors associated with dominant hemisphere lesions.

METHODS EMPLOYED: Speech testing of conscious patients while the exposed brain is being electrically stimulated. Speech testing of patients with dominant hemisphere lesions. Speech testing of patients during aurae and in the post-ictal period.

PATIENT MATERIAL:

		No.	Average Stay - days
Inpatient:	Adult Male	1	48
	Adult Female	3	47
	Child Male	0	
	Child Female	1	48
Outpatient:	Number of patients	0	
	Number of visits	0	

MAJOR FINDINGS: There has been no thorough evaluation of data. Such evaluation as there has been indicates that of the expression speech difficulties, nominative speech is the most severely affected by discharging lesions of the dominant hemisphere. It is probable that receptive difficulties are present but the data are too few for adequate evaluation.

SIGNIFICANCE TO THE PROGRAM OF THE INSTITUTE: One of the programs of the Branch of Surgical Neurology is functional localization in the brain, to which this project specifically applies. This project is allied with one entitled: An Investigation of Speech Function Localized in the Temporal Areas of man of the Branch of Surgical Neurology.

PROPOSED COURSE OF PROJECT: Continuation of collection of data until sufficient is gathered to warrant conclusions.

Budget Data Sheet

10. NINDB-63 (C)
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: RESEARCH

13. NONE

14. NONE

Honors, Awards, and Publications

15.
SERIAL NO.

16. PUBLICATIONS OTHER THAN THIS PROJECT DURING 1955.

NONE

17. HONORS AND AWARDS TO PERSONNEL DURING 1955.

NONE

R.P.C. 1
December 1955 Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
LABORATORY OR BRANCH

3. Clinical Psychology
SECTION

4.
LOCATION (OTHER THAN BETHESDA)

5. NINDB-64 (C)
SERIAL NO.

6. Personality Characteristics of Temporal Lobe Epileptics
PROJECT TITLE

7. Laurence L. Frost
PRINCIPAL INVESTIGATOR

8. Maitland Baldwin, Mildred Blevins, Robert Savard.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

OBJECTIVE: To investigate the personality characteristics of individuals with localized brain damage, particularly in one or the other or both temporal lobes.

METHODS EMPLOYED:
a. Psychological tests of intelligence, personality, learning and abstraction administered to patients with focal epilepsy before and after surgical removal of the epileptogenic focus.
b. Observation of the patients on the ward in numerous situations (e.g. individual conversation, group activities) prior to and following surgical intervention for alleviation of seizures.

PATIENT MATERIAL:

		No.	Average Stay - days
Inpatient:	Adult Male	20	46
	Adult Female	22	45
	Child Male	8	46
	Child Female	9	45
Outpatients	Number of patients	0	
	Number of visits	0	

MAJOR FINDINGS: In the area of personality concerned with the intellect it was found that the non-dominant temporal lobe related to visual-motor skills.While the dominant temporal lobe appears related specifically to language functions. A general temporal lobe function appears to be one of focusing and maintaining attention.

General personality traits prior to surgical removal of the dominant temporal lobe indicate that these people generally have difficulties in handling relations with their fellows even the simpl amenities of ordinary existance are often ignored. Following surgical removal these traits are frequently accented. The role of the non-dominant temporal lobe in personality is unclear, however its removal frequently results in a highlighting of personality defects which existed before surgery.

R.P.C. 1 (a)
December 1955

NINDB-64 (C)
SERIAL NO.

SIGNIFICANCE TO THE PROGRAM OF THE INSTITUTE: Personality defects are commonly seen in those with abnormal temporal lobes (whether seizures result or not). This project is related to one entitled: Mechanism of Memory, Branch of Surgical Neurology.

Budget Data Sheet

10. NINDB 64 (C)
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: RESEARCH

13. NONE

14. NONE

Honors, Awards, and Publications

15.
SERIAL NO.

16. PUBLICATIONS OTHER THAN THIS PROJECT DURING 1955.

NONE

17. HONORS AND AWARDS TO PERSONNEL DURING 1955.

NONE

R.P.C. 1
December 1955 Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness — INSTITUTE
2. Surgical Neurology — LABORATORY OR BRANCH

3. Clinical Psychology — SECTION
4. ______ — LOCATION (OTHER THAN BETHESDA)
5. NINDB-65(C) — SERIAL NO.

6. Intellectual Status with Drug Change in the Cerebral Palsied Child. — PROJECT TITLE

7. Laurence L. Frost — PRINCIPAL INVESTIGATOR

8. Mildred Blevins, J. Gordon Millichap — OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

OBJECTIVES: To determine changes in measured intelligence as various anti-convulsant drugs are used on children with cerebral palsy.

METHODS EMPLOYED: Standardized intelligence tests of the appropriate chronological level are administered to children with cerebral palsy following changing and reestablishing them on various anti-convulsant medications, principally DIAMOX.

PATIENT MATERIAL:

		No.	Average Stay - days
Inpatient:	Adult Male	0	
	Adult Female	0	
	Child Male	3	27
	Child Female	4	25
Outpatient:	Number of patients	14	
	Number of visits	17	

MAJOR FINDINGS: Project recently started and data too few for analysis.

SIGNIFICANCE TO THE PROGRAM OF THE INSTITUTE: To aid in evaluation of anti-convulsant medication particularly of cerebral palsied children to better aid in their schooling.

Budget Data Sheet

10. NINDB-65 (C)
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: RESEARCH

13. NONE

14. NONE

Honors, Awards, and Publications

15. ____________
SERIAL NO.

16. PUBLICATIONS OTHER THAN THIS PROJECT DURING 1955

NONE

17. HONORS AND AWARDS TO PERSONNEL DURING 1955

NONE

R.P.C. 1
December 1955 Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
LABORATORY OR BRANCH

3. Clinical Psychology
SECTION

4.
LOCATION (OTHER THAN BETHESDA)

5. NINDB-66 (C)
SERIAL NO.

6. Intellectual and Social Evaluation of Severely Mentally Retarded Cerebral Palsied Individuals.
PROJECT TITLE

7. Laurence L. Frost
PRINCIPAL INVESTIGATOR

8. Anatole Dekaban
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

OBJECTIVES: To determine more accurate methods of evaluating the social adjustment and intellectual capacity of severely mentally retarded cerebral palsied individuals.

METHODS EMPLOYED: Standardized tests of intelligence and social maturity are administered. The tests analyzed to determine which parts of the tests provide the most valid and reliable estimate of intellectual and social functioning. Using these data further test items are elaborated in order to refine existing tests.

PATIENT MATERIAL:

		No.	Average Stay - days
Inpatient:	Adult Male	2	14
	Adult Female	0	
	Child Male	4	14
	Child Female	0	
Outpatient:	Number of patients	0	
	Number of visits	0	

MAJOR FINDINGS: The project has just been instituted and no findings are available.

SIGNIFICANCE TO THE PROGRAM OF THE INSTITUTE: To provide a more adequate measure of the intellectual and social abilities of severely retarded brain damaged individuals.

PROPOSED COURSE OF PROJECT: Continue the present line of research.

Budget Data Sheet

10. NINDB- 66 (C)
SERIAL NO.

11.
BUDGET DATA

12.
BUDGET ACTIVITY: RESEARCH

13.
NONE

14.
NONE

Honors, Awards, and Publications Sheet

15.
SERIAL NO.

16.
PUBLICATIONS OTHER THAN THIS PROJECT DURING 1955

NONE

17.
HONORS AND AWARDS TO PERSONNEL DURING 1955.

NONE

National Institute of Neurological
 Diseases and Blindness
Surgical Neurology Branch
Section on Developmental Neurology

The Section on Developmental Neurology has been recently formed. The first three months were mainly utilized for the organization of clinical investigation relating to the congenital and early acquired disorders of the CNS and also for the organization of the research neuropathological laboratory. Our staff is not yet complete, and certain items of laboratory equipment must yet be delivered.

Two research projects have just begun; three others are in the preparatory stage as outlined below. Two of the latter projects are rather extensive, and because of the material necessary they call for the participation of other city hospitals. This is imposing special problems and unavoidable delays.

The outline of the five projects is enclosed.

Anatole Dekaban, M. D.

R.P.C. 1
Dec. 1955

ANALYSIS OF NIH PROGRAM ACTIVITIES

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
BRANCH

3. Developmental Neurology
SECTION

4.
LOCATION

5. NINDB-67 (C)
SERIAL NO.

6. The Investigation of the Site and the Extent of Lesions Involving CNS in Cerebral Palsy and Allied Conditions.
PROJECT TITLE

7. Anatole Dekaban, M. D.
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To correlate the clinical picture of the patient with the state of brain as seen in pneumoencephalogram. To obtain some insight into the possible etiology and pathogenesis of the encountered lesions, at least in a proportion of instances.

Method Employed:

1. Genetic investigation.
2. Detailed neurological examination, including psychological testing and EEG.
3. Pneumoencephalogram.
4. Other special tests as indicated.

Patient Material:	No.	Average Stay in Days
Admissions: Children Male	4	14

Major Findings: This is the beginning of the study. Two patients, brothers, showed genetically determined abnormality of the nervous system; third showed early acquired, destructive lesion of one hemisphere, related to or precipitated by a febrile illness. The latter and the fourth patient are still under study.

Significance to Neurological Research: In majority of instances the etiology of cerebral palsy and allied conditions is unknown. Better knowledge of hereditary background, clinical manifestations, as well as the location and extent of the lesion may further our insight into the diverse etiology of these conditions.

PROJECT DESCRIPTION (Continued)

Proposed Course of the Project: This work has just begun. The accumulation of data of such material is necessary and must continue before analysis of findings can be attempted.

R.C.P. - 2
Dec. 1955

Analysis of NIH Program Activities

Budget Data

NINDB-67 (C)
10. SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: RESEARCH

13.

NONE

14.

NONE

Honors, Awards, and Publications

16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

17. HONORS AND AWARDS TO PERSONNELDURING 1955:

R.P.C. - 1
Dec. 1955

ANALYSIS OF NIH PROGRAM ACTIVITIES

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
BRANCH

3. Developmental Neurology
SECTION

4. ____________
LOCATION

5. NINDB-68 (C)
SERIAL NO.

6. Preparation of the Horizons of the Normal Development of the Major Structures of the CNS in Mice.

7. Anatole Dekaban, M. D.
PRINCIPAL INVESTIGATOR

8. Marie Kendall, B. A.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: The main purpose of this work is to supply norms of the gross and microscopic structure of the CNS of mice during progressive stages of prenatal and postnatal development.

Methods Employed:

1. The CNS of mice at 16 progressive developmental stages will be dissected.
2. Representative sections will be prepared and stained.
3. Main structures will be identified and marked on low power microphotographs.

Mice Material:	No. of Stages in Processing
Stock colony of white albino mice.	4

Major Findings: This project has just begun. Brains of eight mice representing four horizons are dissected and are being further processed.

Significance of Neurological Research: An experimental approach to congenital malformations of the CNS is necessary to help understand certain obscure malformations occurring in humans. The provision of norms of the central nervous system has to preceed the experimental production of congenital malformations, as there does not exist any proper guide in the form of an atlas or of a satisfactory reference during consecutive stages of the development.

R.P.C. - 1 (a)
Dec. 1955

NINDB-68 (C)
SERIAL NO.

PROJECT DESCRIPTION (Continued)

Proposed Course of the Project: This work has just begun. The processing of sections from the CNS of mice and the preparation of horizons must continue until completion of all stages.

ANALYSIS OF NIH PROGRAM ACTIVITIES

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
BRANCH

3. Developmental Neurology
SECTION

4. ______
LOCATION

5. NINDB-69 (C)
SERIAL NO.

6. Experimental Production of Congenital Malformations of the CNS.

7. Anatole Dekaban, M. D.
PRINCIPAL INVESTIGATOR

8. Possibly
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: A project is in preparation which relates to the production of congenital abnormalities of the CNS in mice using various noxious agents.

Methods Employed:

1. X-ray radiation of mice during different stages of pregnancy.
2. Utilization of certain enzyme inhibitors during different stages of pregnancy.
3. Gross, skeletal, and microscopic examination of the obtained specimen.

Material: White albino mice.

Findings: This project is in preparation.

Significance to Neurological Research: Morphogenetic and pathological analysis of congenital abnormalities of the CNS at different stages of development will be utilized as an adjunct in explaining similar abnormalities occurring in humans.

Proposed Course of the Project: Collection of material must preceed analysis of findings.

ANALYSIS OF NIH PROGRAM ACTIVITIES

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
BRANCH

3. Developmental Neurology
SECTION

4.
LOCATION

5. NINDB-70 (C)
SERIAL NO.

Principal Investigator from NINDB - Anatole Dekaban, M. D.

PROJECT DESCRIPTION:

In a process of preparation is a joint project with participation of Walter Reed Army Hospital, the Naval Medical Center, and possibly Georgetown University Hospital. The purpose of this investigation is a progressive clinical study of infants who were exposed to undue stress during intrauterine life or during the process of birth. This project cannot be outlined in detail until formally approved by the heads of the respective institutions and until subsequent discussions with the chiefs of the departments concerned will be held.

ANALYSIS OF NIH PROGRAM ACTIVITIES

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Surgical Neurology
BRANCH

3. Developmental Neurology
SECTION

4.
LOCATION

5. NINDB-71 (C)
SERIAL NO.

Principal Investigator: Anatole Dekaban, M. D.

PROJECT DESCRIPTION:

In a process of preparation is a project relating to gross and microscopic examination of the CNS of human embryos, fetuses and stillbirths as well as infants dying early in life. The material will be obtained from the Walter Reed Army Hospital, the Naval Medical Center, and possibly Georgetown University Hospital. The detailed outline of this project has also to await its formal approval by the heads of these Institutions.

R.P.C. - 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Ophthalmology
LABORATORY OR BRANCH

3. Ophthalmology Physiology
SECTION

4.
LOCATION

5. NINDB - 72 (C)
SERIAL NO.

6. Studies on Central Nervous System Control of Intraocular Pressure
PROJECT TITLE

7. Ludwig von Sallmann, M.D. and J. Frank Macri, Ph.D.
PRINCIPAL INVESTIGATOR(S)

8. Theodor Wanko, M.D., Hans Bornschein, M.D. & Miss Patricia Grimes
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: Central nervous influence on intraocular pressure has been the subject of discussion for many years. On the basis of ill-defined clinical observations, it was postulated that the hypothalamus might be involved in disturbances of intraocular pressure regulation. Though this postulate was advanced only minor attempts have been made to establish the validity of this concept.

The present endeavour is to examine this question in a systematic manner under controlled conditions. Of the various sites in the brain which are known to influence autonomic regulation and possibly the intraocular pressure, the hypothalamus and adjacent structures were first examined for two reasons: (1) considerable information is available on this area on other functions, i.e., blood pressure, pupillary size, etc; (2) this area is presumed to be a center of autonomic integration.

In previous communications on this subject it was reported that stimulation of the ventral thalamus and dorsal hypothalamus resulted in isolated rises and falls of intraocular pressure, whereas stimulation of the ventral hypothalamus induced a sympathetic mass discharge with concomitant intraocular pressure changes. In this work no attempt was made to analyze the mechanism of intraocular pressure changes or to identify the receptors, effectors or pathways responsible for these responses. The object of the present study is a critical analysis of the above in addition to mapping of positive stimulation points in other parts of the brain.

Methods Employed: A modified Horsley-Clarke stereotaxic instrument, multichannel Sanborn recording units, a Leeds and Northrup sensitive temperature recorder, a dual beam oscilloscope for electromyography and scaler with a rate meter for recording blood volume changes in the anterior segment of the eye after injection of P-32 labeled red cells, have been assembled for the above mentioned experiment. The experimental animal will be the cat.

Major Findings: Results obtained to date by stimulation of various areas of the posterior hypothalamus and the medial ventral thalamus on intraocular pressure indicate the following: the rise of intraocular pressure is accompanied by a rise of subscleral temperature; the rise is not mediated through the cervical sympathetic nerve; it is not due to mechanical pressure exerted by the striated extraocular muscles; occlusion of the common carotid artery during continuous stimulation causes first a transient fall of intraocular pressure in the homolateral eye, followed by a sustained rise to the pre-occlusion level. Subscleral temperature changes in these cases follow a pattern similar to the intraocular pressure responses; the effect on the intraocular pressure could be abolished by Priscoline and Thorazine.

Significance: Studies of central nervous control of the intraocular pressure present a new phase of glaucoma research. It was brought forward in this year's Josiah Macy Foundation Conference on Glaucoma that experimental evidence for such regulation may have direct clinical implications.

R.P.C. - 3
Dec. 1955

Analysis of NIH Program Activities

BUDGET DATA SHEET

10. NINDB- 72 (C)
SERIAL NO.

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11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1956								
FY 1957								

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12. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

R.P.C. - 4
Dec. 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB- 72 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

R.P.C. - 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Ophthalmology
LABORATORY OR BRANCH

3. Ophthalmology Pharmacology
SECTION

4. ________
LOCATION

5. NINDB - 73 (C)
SERIAL NO.

6. Studies on the Mechanism of Autonomic Drug Action on Intraocular Pressure
PROJECT TITLE

7. Ludwig von Sallmann, M.D., J. Frank Macri, Ph.D.
PRINCIPAL INVESTIGATOR(S)

8. Miss Patricia Grimes
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To determine what role the autonomic nervous system plays in regulation of the intraocular pressure and to determine the mechanism by which such regulation is effected.

Methods Employed: The bilaterality of eye pressure changes influenced by emotions and drug administration as well as normal diurnal variations, point to a neurovascular factor or factors in the regulation of intraocular pressure. Eye pressure is also dependent on changes occurring elsewhere in the body, i.e., heart minute volume, vascular tonus, etc. For these reasons synchronous recordings of variables which have an effect on intraocular pressure, together with eye pressure manometry, offer a new approach to the study of the glaucoma problem on a rational basis.

Multichannel recording with high sensitivity transducers have been developed in the Knapp Laboratory for studies on the intraocular pressure in the last few years. With instrumentation of this type it is possible to compare the effects of drugs on the intraocular pressure of both eyes, the intra-arterial and intra-venous pressure, temperature in the anterior uvea, and the behavior pattern of the pericorneal terminal vasculature, as well as pupils and nictitating membranes. Activity of extra-ocular striated muscles can be determined electromyographically. The apparatus for such study is now assembled in the laboratory for Pharmacology and Physiology, and work on this problem was initiated three months ago with the cat as the experimental animal. It can be said that the present phase of the work confirms the results of previous studies which were limited to eye pressure and blood pressure recordings.

NINDB - 73 (C)
SERIAL NO.

Patient Material:		Number	Average Stay Days
In-Patients:	Adult Males	1	9
	Adult Females	1	57
	Children Males	0	
	Children Females	0	

Out-Patients: Numeber - 10
Number of visits - 31

Significance: Eye pressure responses to autonomic drugs can be elicited by effects on inflow of the aqueous by contraction of the extraocular muscles and particularly by volume changes in the intraocular vasculature. In the present study the influence by neurovascular responses is emphasized. Results of this work should have implication on the problem of eye-pressure pathology (glaucoma).

R.P.C. - 3
Dec. 1955

Analysis of NIH Program Activities

BUDGET DATA SHEET

10. NINDB-73 (C)
SERIAL NO.

11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1956								
FY 1957								

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICIAN ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

R.P.C. - 4
Dec. 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB- 73 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

R.P.C.- 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Ophthalmology
LABORATORY OR BRANCH

3. Ophthalmology Pharmacology
SECTION

4.
LOCATION

5. NINDB-74 (C)
SERIAL NO.

6. Studies on Diet- and Drug-Induced Experimental Cataract
PROJECT TITLE

7. Ludwig von Sallmann, M.D.
PRINCIPAL INVESTIGATOR

8. J. Frank Macri, Ph.D. and Mr. Leo Caravaggio
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: Information obtained by the cytological examination of whole mounts of the lens epithelium after exposure of eyes to ionizing radiation suggested similar studies on diet- and drug-induced lens damage. To find the role played by the lens epithelium in the development of galactose, myleran and tryptophane deficiency cataracts is the immediate objective of this study. Cytological examination of the lens epithelium in combination with histological studies on paraffin sections of such lenses will allow the investigators to determine the sequence of pathological events which ultimately lead to gross opacification of the lens. In particular it will be shown whether injury to the germinative zones of the lens epithelium or primary damage to the lens fibers causes the development of lens opacification.

Methods Employed: The technique of cytological and histological examinations of the animal lenses is the same as described in Project NINDB- in the experiments on ionizing radiations. Experiments on rats and rabbits have been carried out utilizing this procedure.

Major Findings: In galactose lens injury a steep increase of cell division in the lens epithelium precedes the swelling and degenerative changes of superficial lens fibers near the lens equator. Both changes occur before lens opacities can be seen with the biomicroscope. The results of feeding experiments with myleran are incomplete. Tryptophane deficient rats will be available for histological examination in the near future.

Significance: By systematic histological examination both in vivo, by biomicroscopy and particularly by cytological and histological examinations at various time intervals after introduction of the cataractogenic agents or dificiencies, it can be expected that similarities and differences in the pathogenesis of various types of experimental cataracts will be established which in the future might be correlated with chemical studies. Knowledge of the pathogenesis of various types of cataract might permit a rationale for therapeutic intervention.

R.P.C. - 3
Dec. 1955

Analysis of NIH Program Activities

BUDGET DATA SHEET

10. NINDB- 74 (C)
SERIAL NO.

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11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1956								
FY 1957								

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12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW AND APPROVAL ☐ TECHNICIAN ASSISTANCE ☐

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13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

R.P.C. - 4
Dec. 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB- 74 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

R.P.C.- 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Ophthalmology
LABORATORY OR BRANCH

3. Ophthalmology Histopathology
SECTION

4. ____________
LOCATION

5. NINDB-75 (C)
SERIAL NO.

6. Effects of Ionizing Radiations on the Lens of Various Species of Experimental Animals
PROJECT TITLE

7. Ludwig von Sallmann, M.D. and Mr. Leo Caravaggio
PRINCIPAL INVESTIGATORS

8. ____________
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: Work which has been carried out in the past 5 years in various laboratories on the effect of several types of ionizing radiations on the lens indicates that the radiosensitivity of the crystalline lens to such radiations varied with different species. The object of the present study is to provide a possible explanation for these differences as far as it can be established on morphological grounds. Since the lens epithelium is a sensitive indicator for early radiation damage, the response of this cell layer to intravenously induced P-32 might yield data pertaining to the feasibility of the use of this isotope for turnover studies and possibly to the risks involved in tracer work.

Methods Employed: Whole mounts of lens epithelium are excellently suited for quantitation of mitotic activity and radiation-induced cell degeneration, since the entire population of the monolayer epithelium can be examined and the second non-irradiated lens can be used as an ideal control. The mitotic index per preparation in different zones of the epithelium can be determined in various species, at various age groups, and the changes can be followed for prolonged periods after exposure to the radiation sources by terminating the experiments at desired intervals.

Paraffin imbedded lenses of other identically treated animals are studied histologically to render information on the migration of epithelial cells into remote areas of the lens and their participation in cataract formation. Results of in vivo observations on the animal can be correlated with the cytological and microscopic findings. Mice, rats, guinea pigs, rabbits, cats, dogs, and rhesus monkeys are the experimental animals.

The experiments with P-32 are conducted on litter mates (rabbits) with various time intervals allowed to elapse before sacrificing the animals.

Major Findings: The mitotic rate in the lens epithelium of the mouse per 100,000 cells is the highest (101), that of the rhesus monkey the lowest (2.9), among the species under study. The radio-sensitivity of these lenses appear to depend directly upon this function. Duration of post irradiation depression of mitosis does not seem to reflect the degree of radiation sensitivity; nor does the number of degenerative cells express necessarily the degree of radio vulnerability of the lens. In order to clarify the situation, it is necessary to study both epithelium and lens fibers in prolonged experiments. This part of the work is well under way but not completed.

The mitotic index of the lens epithelium varies greatly with age and parallels in limits the radio-sensitivity of various age groups. The degenerative changes of the cells in old age (rats) are strikingly similar to those induced by ionizing radiation. At the present time human lenses removed for cataract are being studied to compare the cytology of senile cataract with that of radiation cataract.

Significance: The described studies might lead to a better understanding not only of radiation induced lens damage but also to the pathogenesis of senile cataract.

R.P.C. - 3
Dec. 1955

Analysis of NIH Program Activities

BUDGET DATA SHEET

10. NINDB- 75 (C)
SERIAL NO.

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11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1956								
FY 1957								

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12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICIAN ASSISTANCE ☐

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13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

R.P.C.-4
Dec. 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-75 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

R.P.C. - 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Ophthalmology Branch
LABORATORY OR BRANCH

3. Ophthalmological Disorders Service
SECTION

4. ____________
LOCATION

5. NINDB-76 (C)
SERIAL NO.

6. Evaluation of Newer Steroids in the Treatment of Experimental and Clinical Uveitis.
PROJECT TITLE

7. James F. O'Rourke, M.D.
PRINCIPAL INVESTIGATOR(S)

8. Gilbert Iser, M.D.; Monte G. Holland, M.D.; George Goodman, M.D. and G. Richard O'Connor, M.D.
OTHER INVESTIGATOR(S)

9. PROJECT DESCRIPTION:

Objectives: A comparison of prednisone anti-inflammatory effects with those of cortisone and hydrocortisone in experimental and clinical uveitis therapy.

Methods Employed:

Basic Study.

1. Induction of horse serum uveitis in previously sensitized animals followed by the intramuscular injection of either prednisone, cortisone, hydrocortisone or ACTH.

2. An estimation of the uveitis response to each separate steroid treatment regimen based on grading of lesions according to the severity of:
   (a) keratitic precipitates
   (b) aqueous cellularity
   (c) aqueous beam
   (d) iris hyperemia.
   Control animals treated with intramuscular saline injection.

3. Series of lesions treated to demonstrate steroid effects both in blocking the onset of subsequently induced uveitis and in the treatment of established lesions.

Clinical Studies. Prednisone is employed in the therapy of anterior and posterior uveitis, plus optic and retrobulbar neuritis. Observations of the speed and adequacy of response following local and systemic therapy will be compared to the results of previous steroid therapy, in each individual case. The basic uveitis studies for etiologic diagnosis include x-ray, skin testing with indicated antigens and specific blood studies for hematologic and blood chemistry alterations.

Patient Material:		Number	Average Stay Days
In-Patients:	Adult Males	6	56
	Adult Females	4	27
	Children Males	0	0
	Children Females	0	0
Out-Patients:			
	Number	18	
	Number of Visits	246	

Major Findings:

1. Basic studies of animal uveitis response to prednison therapy indicate a potency approximately five times that of other steroids. Ultimate clearing time of inflammation, however, is not greatly shortened, nor is the onset of anti-inflammatory effect noticeably hastened.

2. On clinical trial prednisone has not to date exceedec the anti-inflammatory effects of cortisone or hydrocortisone given in therapeutic doses. The dose required per patient, however, is much lower and the incidence of serious side effects was negligible

3. The specificity of response noted in several patients to only certain steroids raises the possibility of a tissue selectivity.

4. Prednisone has been found effective when combined with specific anti-toxoplasmic chemotherapy in the treatment of granulomatous uveitis in several instances. Thus has an overlapping of projects between the toxoplasmosis study and the steroic evaluation project been effected.

Significance to Institute Program: Two factors of general clinical interests have emerged: (1) the inability of prednisone to exceed the response which follows other steroid therapy, and (2) the selectivity of response to various steroids among the patients studied. These factors may well apply to other areas of the Institute in which such treatment is employed.

Encouraging results noted on the combination of steroid therapy with specific chemotherapy has special reference to uveitis studies in Ophthalmology. As such they will motivate further comparative evaluation studies with currently accepted regimens of uveitis treatment.

Proposed Course of Project: Continued clinical evaluation of all steroids both alone and in combination with specific chemotherapy is contemplated in the treatment of granulomatous uveitis.

R.P.C. - 4
Dec. 1955

Analysis of NIH Program Activities

BUDGET DATA SHEET

10. NINDB- 76 (C)
SERIAL NO:

11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1956								
FY 1957								

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICIAN ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

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R.P.C. - 5
Dec. 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB- 76 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

"An Initial Evaluation of Prednisone Therapy in Ocular Inflammation", by James F. O'Rourke, M.D., Gilbert Iser, M.D. and Ralph W. Ryan, M.D. Accepted for publication by A.M.A. Archives of Ophthalmology in 1955.

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

R.P.C. - 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases & Blindness
INSTITUTE

2. Ophthalmology Branch
LABORATORY OR BRANCH

3. Ophthalmology Physiology
SECTION

4. ____________
LOCATION

5. NINDB-77 (C)
SERIAL NO.

6. Detection of Ocular Tumor by Isotope Methods.
PROJECT TITLE

7. James F. O'Rourke, M.D.
PRINCIPAL INVESTIGATOR(S)

8. ____________
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives. This project seeks to evaluate current isotope tracer studies undertaken for ocular tumor diagnosis and to develop more accurate methods based on these techniques.

Methods Employed: The studies will be of both (1) clinical and (2) basic types.

1. Clinical. Patients in the following categories, likely to conceal or simulate a malignancy, are accepted for study: (a) retinal detachment, solid or serous; (b) unilateral exophthalmos; (c) progressive or non-responsive lesions of the lid and lacrimal apparatus; (d) cysts and tumors of the iris; (e) blind phthisical eyes; and (f) retinoblastoma suspects.

Patients accepted after preliminary screening examination are given intravenous tracer doses of radioisotopes, following which both external and posterior counting of detectible emissions may be carried out. For this purpose, specially designed Geiger-Mueller and scintillation type counting probes have been devised and are available. Counts are taken over both eyes on a quadrant basis at one-hour and 24-hour intervals.

2. Basic Studies. Tissue analyses of S-91 malignant melanomas of mice are carried out on acid digests of tumor and normal tissues, at various time intervals following the intravenous injection of radioactive isotopes. Calculations of the relative uptake and retention of the isotope by tumor tissue are based on the counts per minute obtained from suitably prepared dry samples of the tissue digests.

Simultaneous activation analysis studies of animal tumor tissue by neutron bombardment are underway at the Oak Ridge National Laboratory, Division of Analytical Chemistry, in an effort to determine which inorganic ions are present and operative in melanoma metabolism.

Patient Material:		Number	Average Stay Days
In-Patients:	Adult Males	1	22
	Adult Females	3	20
	Children Males	1	1
	Children Females	0	0
Out-Patients:			
	Number -	3	
	Number of Visits -	8	

Major Findings: The progress of this project thus far is to be reported in three categories: (1) equipment, (2) clinical studies, and (3) basic studies.

1. Equipment.

Geiger-Mueller Counters - Acquisition of two special probes designed for ocular counting makes possible the application of both external and surgical (retrobulbar) techniques.

Scintillation Counter - Parts for special collimated scintillation counter and gamma spectrometer system have been assembled with significant economy by collaboration of efforts with the Oak Ridge National Laboratory, Physics Division. The principles of focusing collimation and pulse height analysis operative in the system permit greater resolution and exclusion of scattered radiation in gamma ray counting than was previously possible.

Gamma source uptake and localization studies will be carried out on both animal and human subjects in an effort to evaluate the performance of this equipment for tumor localization.

2. Clinical Studies. Both external and retrobulbar ocular P-32 counting services are now available for suitable patients. To date many anatomical and physical limitations of beta source counting have become apparent: both primary and metastatic ocular malignancies have escaped detection on the basis of P-32 uptake in our studies. This has served to motivate a continued search for suitable gamma emitting sources. Two papers are in preparation dealing with such limitations of P-32 counting.

3. Basic Studies. Radioactive phosphorus uptake by normal animal eyes and by S-91 malignant melanoma include the following categories:

A. Normal eyes.
   (1) The percentage of administered P-32 present in the animal globe at one- and 24-hour intervals following intravenous injection (completed).
   (2) The role of extraocular muscle and fascial tissues on in vivo P-32 counting (completed).
   (3) Scleral absorption ratio of intraocular P-32 emission (completed).
   (4) The effect of intraocular and extraocular inflammation on P-32 uptake (in progress).
   (5) P-32 uptake of component ocular tissues (pending).

B. Animal S-91 Melanoma Studies.
   (1) The Differential Absorption Ratio of P-32 in malignant melanoma of mice (completed).
   (2) Activation analysis of S-91 melanoma, plus gamma and beta spectrometric studies for inorganic ion makeup of melanoma (in progress at Oak Ridge).
   (3) Uptake of gamma emitting isotopes by S-91 mouse melanoma (pending).

Significance to Institute Program: The construction and evaluation of newer tumor localizing equipment will yield results applicable to other NINDB studies dealing with malignant disease.

Clinical studies of non-malignant ocular disease by the use of isotopically tagged antibodies will in all probability overlap tumor localization procedures with regard to equipment required for counting of high resolution.

Proposed Course of Project: 1. Continuation of P-32 counting techniques applied to referred patients, pending the completion of basic studies on gamma emitting sources. 2. The evaluation of gamma uptake by animal tumors. 3. The improvement of gamma counting resolution.

R.P.C. - 5
Dec. 1955

Analysis of NIH Program Activities

BUDGET DATA SHEET

10. NINDB- 77 (C)
SERIAL NO.

11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1956								
FY 1957								

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICIAN ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

R.P.C. - 6
Dec. 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB- 77 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Ophthalmology
LABORATORY OR BRANCH

3. Ophthalmology-Physiology
SECTION

4.
LOCATION

5. NINDB-78 (C)

6. The Influence of Hypothermia on the Electrical Responses of the Visual System.
PROJECT TITLE

7. Hans Bornschein, M.D.
PRINCIPAL INVESTIGATOR(S)

8. Gilbert Iser, M.D., George Goodman, M.D. and Ralph Gunkel, O.D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To determine the influences of hypothermia on the electroretinogram using a hibernating animal (hamster).

Further steps will be the comparison of the effects of hypothermia and anoxia on the electroretinogram and the electrical activities of the retinal ganglion cells and optic nerve.

Methods Employed: The electroretinogram in the anesthetized hamster will be picked up with a special contact lens electrode during stimulation with single light flashes and/or flicker light of various intensities, and in various states of adaptation. Measurements will be made with a twin beam oscilloscope and appropriate preamplifiers. The body temperature will be varied by circulating water through copper coils between which the animals are placed. The temperature of the head will be measured in the cheek-pouch. The effect of acute anoxia (ligation of aorta) will be studied at various temperature levels.

Significance to Institute Program: In the last few years the human electroretinogram has gained clinical importance, although the diagnostic value is still a matter of discussion. The electroretinogram is the result of various potentials of different signs, the origin and significance of which are controversial. In order to understand the clinical electroretinogram it is necessary to obtain more basic data along the lines of analysis of the components of the electroretinogram.

Proposed Course of Project: At first it is proposed to study only the effect of hypothermia on the electroretinogram (using the hamster), with variation of the stimulus conditions (intensity etc.) Further studies will include the recording of retinal ganglion cell activity and/or optic nerve impulses. This latter work will probably have to be done in larger animals such as the cat, with controlled circulation.

R.P.C. 3
Dec. 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-78 (C)
SERIAL NO.

11. BUDGET DATA:

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1956								
FY 1957								

12. BUDGET ACTIVITY:

RESEARCH ☐
ADMINISTRATION ☐
REVIEW & APPROVAL ☐
TECHNICIAN ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 OR 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S) (ITEM 1).

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R.P.C. 4
Dec. 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-78 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

R.P.C. - 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases & Blindness
INSTITUTE

2. Ophthalmology Branch
LABORATORY OR BRANCH

3. Ophthalmology Physiology
SECTION

4.
LOCATION

5. NINDB-79 (C)
SERIAL NO.

6. The Effect of Rate of Rise of Photic Stimuli on the Human Electroretinogram.
PROJECT TITLE

7. Hans Bornschein, M.D.
PRINCIPAL INVESTIGATORS

8. Ralph D. Gunkel, O.D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objective: To study the qualitative and quantitative changes in the components of the human ERG, produced by varying the rate at which the light stimulus reaches its full intensity.

Methods Employed: The material will be normal subjects. The ERG is obtained by a contact glass electrode from the anesthetized eye. The recording is made while the subject's eye is exposed to a light stimulus.

Major Findings: None to date.

Significance to Institute Program: The rate of rise of the light stimulus is the only stimulus factor which has not been investigated in its effect on the ERG. It would be expected that this study would contribute to an analysis of the different waves of the human ERG. Such an investigation is particularly interesting, because the factor of the rate of rise of a stimulus is so important in electrical stimulation of the nerve ("accommodation" of the nerve).

R.P.C. - 2
Dec. 1955

Analysis of NIH Program Activities

BUDGET DATA SHEET

10. NINDB- 79 (C)
SERIAL NO.

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11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1956								
FY 1957								

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12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICIAN ASSISTANCE ☐

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13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

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R.P.C. - 3
Dec. 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB- 79 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Ophthalmology
BRANCH

3. Physiology
SECTION

4.
LOCATION

5. NINDB- 80 (C)
SERIAL NO.

6. Evaluation of Electroretinography as a Useful Clinical Tool.
PROJECT TITLE

7. Gilbert Iser, M.D., and George Goodman, M.D.
Principal Investigators

8.
Other Investigators

9. PROJECT DESCRIPTION:

Objectives: Electroretinography is the study of the electrical potentials elicited from the retina by a light stimulus. It affords the ophthalmologist an objective index of retinal function. Karpe (1945) suggested the use of a single flash light stimulus after several minutes of dark adaptation as the standard procedure in clinical studies, and this is the method which has been used by clinical investigators. However, there are many limitations to the use of the Karpe method. Large areas of central and peripheral retina may be damaged and yet the electroretinogram remains normal. In addition, as it is usually recorded in the dark-adapted eye, the electroretinogram is dominated by rod potentials and poorly reflects cone function.

The success obtained with subjective flicker fusion frequency tests in revealing minimal retinal lesions suggests the study of the objective flicker fusion frequency by electroretinographic means. Furthermore, recent experiments with the use of a high intensity flickering stimulus have shown that the resulting photopic flicker electroretinogram is primarily a response of the retinal cones. This indicates that the high intensity flicker electroretinogram may be affected abnormally by macular disease and diseases of the cone system where the single flash electroretinogram is not.

The present study was undertaken to determine whether the flicker electroretinogram would provide more diagnostic information than the standard single flash electroretinogram in ocular disease and other choreoretinal affections.

Methods Employed: Patients are tested while resting in bed. The Grass Photic Stimulator is used as a flashing light source, and the patients are tested with stimuli of varying intensity, frequency, and wavelength. The potentials are picked up simultaneously from bot eyes with contact lens electrodes, and the binocular recordings are made on a Grass eight-channel direct writing electroretinographic machine.

Patient Material:		Number	Average Stay Days
In-Patients:	Adult Males	0	0
	Adult Females	1	39
	Children Males	0	0
	Children Females	1	38
Out-Patients:	Number	12	
	Number of Visits	43	

Patients suitable for study are drawn from those referred to the Ophthalmology Branch for investigation. Patients with normal eye findings are used as controls and those with retinal detachment, hereditary, inflammatory and vascular retinopathies are studied for diagnostic changes. Approximately 75 patients were studied electroretinographically during the past year.

Major Findings: During the past nine months the equipment was assembled and tested. The electroretinographic tracings on normal controls are comparable to those obtained by other investigators.

Patients with retinal disease were tested with scotopic and photopic single flash techniques. A depressed electroretinogram was found in cases of severe myopia and diabetic retinopathy, extensive posterior uveitis, retinal detachment, and marked color deficiency. The degree of electroretinographic abnormality appears to be dependen upon the area of retina involved and the type and degree of structura or functional damage which has occurred.

Preliminary investigations with flicker electroretinography were carried out using high intensity white light stimuli. The amplitude of the flicker waves and their fusion frequency are decreased in cases with diffuse retinal disease. Further studies with the flicker electroretinogram and the use of different stimulating intensities and wavelengths are under way.

Significance to Institute Program: Ophthalmologists have long sought more accurate methods of determining retinal function, especially macular integrity, in the presence of opacities of the ocula media. The answer to this search may lie in the development of new techniques of electroretinography.

R.P.C. - 3
Dec. 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB - 80 (C)
SERIAL NO.

11. ______________________________
BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1956								
FY 1957								

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICIAN ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 OR 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

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R.P.C. - 4
Dec. 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB- 80 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

R.P.C. - 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Ophthalmology Branch
LABORATORY OR BRANCH

3. Ophthalmology Bacteriology
SECTION

4.
LOCATION

5. NINDB- 81 (C)
SERIAL NO.

6. The Diagnosis and Treatment of Ocular Toxoplasmosis
PROJECT TITLE

7. G. Richard O'Connor, M.D.
PRINCIPAL INVESTIGATOR(S)

8. Chie Tanaka, M.D.; Leon Jacobs, Ph.D. (NMI)
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Current histological and serological studies now intimate that 20-25% of all uveitis (chorioretinitis and iritis) may be due to infection with the Protozoan parasite Toxoplasma gondii. Judging from the presence of neutralizing antibodies in the blood stream of large segments of the population, it is assumed that many people either have the disease in chronic subclinical form, or have been exposed to it at some time in the past, in a manner analogous to tuberculosis.

The chorioretinal lesion, as seen with the ophthalmoscope, is difficult to differentiate from other forms of granulomatous uveitis such as tuberculosis, brucellosis, tularemia, syphilis, etc. It has been shown in known cases of ocular toxoplasmosis, where the organism has actually been recovered from the enucleated eye, that the so-called Toxoplasma dye test, the mainstay of our present diagnostic regimen, is not truly reliable as an indicator of specific ocular infection.

Objectives: To find more specific methods for the diagnosis of ocular toxoplasmosis. To determine through scrutiny of the patients' medical history and serological evidence the various factors of etiological significance in the acquisition of the disease. To observe the pathogenesis of the ocular disease and its response to various forms of therapy.

Methods Employed: Two new approaches have been made to the diagnosis of the ocular disease. Both are directed toward the use of specific Toxoplasma antibody in the detection of the infection.

(a) The agar-diffusion method for the detection of anti-Toxoplasma precipitins in the eye: In addition to the presence of neutralizing antibodies (Dye Test Antibodies) and complement-fixing antibodies to Toxoplasma, it is thought that there are also precipitins for Toxoplasma in immune sera. The purpose of the agar-diffusion method is to detect precipitin reactions under conditions where small volumes of antibody-containing fluids, such as aqueous humor, are used. It is thought that in infectious diseases of the uveal tract, antibody formation takes place in the eye in excess of that which reaches the interior of the eye through permeation of the blood-aqueous barrier. Precipitins present in the aqueous humor should be detectable when samples of aqueous are allowed to diffuse through a semi-solid clear agar gel toward an opposing body of antigen molecules. Opaque lines of precipitate should be seen at the interface between the diffusing antigen and antibody whereas little as 10 micrograms per ml. antibody nitrogen is present.

(b) The detection of labelled Toxoplasma antibody in the chorioretinal lesions of living eyes: Anti-Toxoplasma rabbit serum with a dye test titer of 1:250,000 has been prepared. This method involves the labelling of such antibody with fluorescein, an azo-dye, or radioactive iodine. Antibody so labelled and injected parenterally can be expected to localize in the eye lesion at the site of antigen liberation. Here it should be detected by the use of ultraviolet light, direct ophthalmoscopy, or a Geiger counter respectively.

Patient Material:		Number	Average Stay Days
In-Patients:	Adult Males	5	17
	Adult Females	11	27
	Children Males	1	31
	Children Females	4	24
Out-Patients:	Number	42	
	Number of Visits	292	

Granulomatous uveitis cases are obtained by physician referral. Screening for the presence of high Toxoplasma dye test titers or toxoplasmin skin reactions can be done before the selection of the patient. Those patients with evidence of anterior involvement of the eye are of particular interest for aqueous study.

Major Findings: The presence of precipitins in Toxoplasma antisera of known high dye test titer was determined using the standard tube dilution method. The reaction seems to be pH sensitive, occurring most readily at pH 6.5. It does not occur in the presence of active complement. No discrete precipitin lines have been observed in agar as yet, but the buffer system and electrolyte content may have to be altered to obtain optimal reactions.

Rabbit gamma globulin preparations of high purity have been made through the use of an electro-convection apparatus. There is evidence that antibody activity is preserved through this particular method of preparation.

Supra-choroidal injections in the rabbit's eye have been made using the technique of Vogel. It is planned to establish posterior pole infections in the rabbit's eye preparatory to the use of labelled antibody.

Significance to Institute Program: There is good evidence that at least in the earlier or acute phases of ocular toxoplasmosis, treatment with Pyrimethamine, Sulfa drugs, and the anti-inflammatory agents such as ACTH or Cortisone has resulted in the halting of a progressive uveitis and the restoration of useful vision. If a more specific diagnosis could be made at the onset, much valuable time might be saved for the patient if he is treated with anti-Toxoplasma drugs, as opposed for example, to six months of anti-tuberculous therapy or one year of tuberculin desensitization. Many cases of ocular toxoplasmosis have undoubtedly gone undiagnosed because of the lack of even the more rudimentary serological aids to diagnosis.

The agar-diffusion technique also offers a good possibility for the diagnosis of other types of uveitis using a series of many different antigens. In this regard it might be a truly fundamental gain in the otherwise highly dubious current etiologic diagnoses of uveitis.

Proposed Course of Project: To proceed with the labelling of the purified rabbit gamma globulin, first with fluorescein and then with the other afore-mentioned agents. To test the predilection of labelled antibody for the artificially induced Toxoplasma lesion in the rabbit's iris. To test its predilection for posterior pole lesions in the rabbit and then in man.

We will continue to observe and treat patients with presumed toxoplasmic uveitis, with special emphasis on the information to be gained from paracentesis and examination of the aqueous humor, response to drug therapy, and eventually for detection of toxoplasmic lesions *in situ*.

Present Status: Active cases are now available for investigation. Purified rabbit anti-Toxoplasma globulin has been prepared. Precipitins to Toxoplasma have been demonstrated in serum by the serial tube dilution method, but not as yet by the agar-diffusion method.

R.P.C. -4.
Dec. 1955

Analysis of NIH Program Activities

BUDGET DATA SHEET

10. NINDB-81 (C)
SERIAL NO.

11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1956								
FY 1957								

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW AND APPROVAL ☐ TECHNICIAN ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S). (ITEM 1)

Doctor Leon Jacobs of the National Microbiological Institute, Laboratory of Tropical Diseases, is carrying on animal, tissue culture, and epidemiological studies on Toxoplasma gondii in cooperation with our branch. He furnishes facilities and supervision for the toxoplasma dye test, complement fixation test, and for the production of human skin-test antigen from the peritoneal exudate of infected mice. He supplies us with high titer rabbit anti-serum. He performs the standard dye test on gamma globulin fractions which are to be tested for antibody activity. He handles the inoculation of animals with suspected infectious samples of aqueous humor and other tissues. Miss M. K. Cook, who is in the employ of the Ophthalmology Branch of NINDB, is directly associated with Doctor Jacobs in his laboratory. In addition to assisting with the dye test and routine animal work, she is pursuing experiments on the tissue culture of Toxoplasma in the rabbit retina.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES, OR FUNDS) IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH.)

This complements animal experimentation carried on by Doctor Don Eyles at the Memphis Public Health Service facility.

R.P.C. - 5
Dec. 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB- 81 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

R.P.C. - 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases & Blindness
INSTITUTE

2. Ophthalmology Branch
LABORATORY OR BRANCH

3. Ophthalmology Bacteriology
SECTION

4. ____________
LOCATION

5. NINDB- 82 (C)
SERIAL NO.

6. Study of Viruses Affecting the Eyes
PROJECT TITLE

7. Chie Tanaka, M.D.
PRINCIPAL INVESTIGATOR(S)

8. G. Richard O'Connor, M.D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To study the cultivation of trachoma virus. To study the cultivation of epidemic keratoconjunctivitis virus. To study the relationship between A.P.C. and E.K.C. virus. To culture viruses, if possible, from cases of uveitis of unknown etiology.

Methods Employed: Investigators for this project are experimenting with the cultivation of the trachoma virus and E.K.C. virus in conjunctival epithelial cell culture. Because trachoma is an epithelial disease, the virus thrives especially well in conjunctival epithelium. This study will be continued in an attempt to isolate the virus. It is of primary importance in this experiment to work with fresh cases of trachoma with numerous inclusions. Doctor Yukihiko Mitsui of Kumamoto, Japan, member of W.H.O. Expert Advisory Panel on Trachoma has consented to provide these clinical specimens.

After isolation of the viruses the following methods of identification will be employed:

1. Demonstration of serological relationship of isolated viruses to trachoma and E.K.C.

2. Study of the biologic properties of both viruses: their stability, their resistance to antibiotics, their filterability, their pathogenicity for laboratory animals and their productivity of soluble toxin.

3. Reproduction of experimental trachoma in monkeys or apes.

In attempting to culture viruses from cases of uveitis, aqueous humor samples will be innoculated into tissue cultures of epithelial cells, and cytopathic changes will be observed.

Patient Material: Material from active trachoma with numerous inclusions and active cases of epidemic kerato-conjunctivitis are preserved by dry freezing and transported by air from Doctor Yukihiko Mitsui, Kumamoto, Japan.

Major Findings: The cytopathogenic effects of A.P.C. viruse in the conjunctival epithelial cells resemble those described for He La cells. Maintenance medium for the cultivation of the A.P.C. virus in the conjunctival epithelial cell culture was found to be a mixture of 10% horse serum and 90% Eagles He La growth media.

Significance to Institute Program: Trachoma is a universal problem. Temporary control can be obtained with antibiotics and improvements in sanitary conditions. Cultivation of the trachoma virus becomes an urgent demand and will aid in ultimate control of the disease. The trachoma committee of W.H.O. is interested in promoting studies in this area.

The significance of virus culture studies on uveitis might be very great since a definite etiological diagnosis can rarely be made in present day studies of uveitis. If virus cultures were positive, much of the guess-work in current diagnosis might be eliminated by a laboratory test.

R.P.C. - 3
Dec. 1955

Analysis of NIH Program Activities

BUDGET DATA SHEET

10. NINDB- 82 (C)
SERIAL NO.

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11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1956								
FY 1957								

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12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICIAN ASSISTANCE ☐

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13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

R.P.C. - 4
Dec. 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB- 82 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

R.P.C. - 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Ophthalmology Branch
LABORATORY OR BRANCH

3. Ophthalmology Histopathology
SECTION

4. ____________
LOCATION

5. NINDB- 83 (C)
SERIAL NO.

6. Study on the Innervation of the Anterior Chamber Angle
PROJECT TITLE

7. Monte G. Holland, M.D.
PRINCIPAL INVESTIGATOR(S)

8. Mrs. Eleanor Collins and Ludwig von Sallmann, M.D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: There is a considerable amount of evidence that a neurovascular mechanism is operative in the eliciting of glaucomatous attacks and contributing to factors which regulate the inflow and outflow of the aqueous humor. Attention was drawn again recently by Ernst Barany to the cellularity in the trabecular network and the possibility that this structure is not an inert filter but physiologically reacting tissue. Vrabec in a recent study has demonstrated the presence of nerves in this general area in several species of vertebrate animals but fails to show the termination of these nerves and their connections with Schlemm's canal. In view of the importance of the trabeculum in regulating the outflow of the aqueous humor and thus in participation in the control of intraocular pressure, it is the purpose of the present project to systematically investigate the innervation of the trabeculum, Schlemm's canal and outlet channels in several vertebrate species. This study, then, is in line with the work on central nervous influences on the intraocular pressure, since it deals with the search for receptors and effectors for nervous stimuli.

Methods Employed: The methods used are the silver-staining techniques, particularly the Gros-Schultze modification of Bielschowsky's stain and newer silver impregnating methods which will be compared with the effect of the results obtained with the methylene blue technique. By sectioning the trabeculum in various planes it is anticipated that silver impregnation and methylene blue staining will selectively demonstrate the nerves and permit a close study of the anatomy and the morphology of the nerve endings in the trabeculum and outlet channels.

The studies are to be carried out on human eyes when they become available. It is contemplated that monkeys, cats, rabbits, dogs and birds will be the experimental animals.

Major Findings: As the study is at present in a preliminary stage, it is not possible to state any conclusive findings. However, eyes of several cats, rabbits and monkeys have been studied, using the methods outlined and it has been possible to trace nerves running into the trabeculum, which apparently terminate there. To fully delineate the morphology of the delicate nerve endings will not be possible until the technique of staining and impregnation has been perfected.

Significance to Institute Program: If the innervation of the components of the trabeculum can be established on morphological grounds it will offer a new piece of evidence indicating how nervous impulses may be mediated in regulating the intraocular pressure. It would be of fundamental importance in particular with reference to the neurovascular mechanisms involved in regulating the intraocular pressure and also have significance in reference to the glaucoma problem. Evidence has steadily accumulated indicating that the trabeculum, Schlemm's canal and collector channels are extremely important in the regulation of the normal intraocular pressure and also the probable site of resistance to aqueous outflow in glaucoma. Through the systematic study of the innervation of these structures, it is hoped that a morphological basis will be found to complement the understanding of the basic physiology of the outflow mechanism.

R.P.C. - 3
Dec. 1955

Analysis of NIH Program Activities

BUDGET DATA SHEET

10. NINDB- 83 (C)
SERIAL NO.

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11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1956								
FY 1957								

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12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICIAN ASSISTANCE ☐

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13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

R.P.C. - 4
Dec. 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-83 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

R.P.C. - 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Ophthalmology Branch
LABORATORY OR BRANCH

3. Ophthalmology Physiology
SECTION

4. ____________________
LOCATION

5. NINDB- 84 (C)
SERIAL NO.

6. Improvement in the Design and Construction of Ophthalmic Instruments.
PROJECT TITLE

7. Ralph D. Gunkel, B.S., O.D.
PRINCIPAL INVESTIGATOR(S)

8. ____________________
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To make improvements in the instruments used in ophthalmic examination or treatment.

Specifically: To make final improvements in the magnetically controlled self-recording tangent screen device mentioned in the last report.

To adapt a non-varying, non-flickering light source to the Bausch and Lomb retinal camera for greater uniformity in pictures than is now possible with the carbon arc light.

To develop a clinically useful flicker fusion field testing device and technique.

To develop other devices, instruments, or techniques as needs and situations arise.

Major Findings: The tangent screen device has probably been improved to its ultimate state of refinement and could be produced commercially in its present form. The marking device formerly causing some difficulty has been simplified to a pneumatic plunger and bulb which does not fail to function. Since a uniform illumination of seven foot-candles is desired for standardizing central visual fields, it was considered necessary to design a suitable light source. This was done, using a 16-inch circular fluorescent tube with a variable shutter arrangement. This also provides for more sensitive tests by reducing the illumination to less than seven foot-candles if desired.

A 100 watt zinconium arc lamp has been adapted and installed in place of the carbon arc lamp on the Bausch and Lomb retinal camera. It has been found to give usable Kodachrome pictures with one-half and one-fifth second exposures. It is currently being tested with Anscochrome film, which it is believed will give better pictures with shorter exposure time.

Instruments have been assembled and some work has been done toward developing a new flicker-field technique. A Sylvania glow modulator tube with its square wave generator, lens, and filter system appear to elicit more definite responses from the subject than were formerly possible.

A transparent plastic electrode holder has been constructed for electroretinography and found to be satisfactory. It provides positive contact, visible electrodes, and eliminates the need for using tape as was formerly done.

Numerous requests have been received and met for the construction of plastic shields, pads, and lens holders individually designed for special cancer patients.

Significance to Institute Program: It is believed that the tangent screen device developed here provides the most convenient, rapid and reliable means yet available for the measurement of central visual fields. Its use is now accepted as standard procedure in our Eye Clinic.

While it is not possible to strictly evaluate devices or ideas contributed to electroretinography and other projects, it is believed that they are considered definitely helpful.

Proposed Course of Project: A project of this type must have sufficient flexibility to permit collaboration with new workers and in new projects. Present plans call for continuation of this project along lines similar to those of the past year, with modifications to meet needs and situations as they arise.

R.P.C.-3
Dec. 1955

Analysis of NIH Program Activities

BUDGET DATA SHEET

10. NINDB-84 (C)
SERIAL NO.

11. ________________________________
BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1956								
FY 1957								

12. BUDGET ACTIVITY:

RESEARCH	☐	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	TECHNICIAN ASSISTANCE	☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 OR 1957: IF COOPERATING UNIT IS WITHIN NIH INDICXTE SERIAL NO(S) (ITEM 1).

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

R.P.C. - 4
Dec. 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB- 84 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

The tangent screen device was presented at the Chicago convention of the American Academy of Ophthalmology in October.

"A Self-Recording Remote Control Tangent Screen", by Ralph D. Gunkel, M.S., O.D. and Ralph W. Ryan, M.D. American Journal of Ophthalmology (in press).

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Ophthalmology
LABORATORY OR BRANCH

3. Ophth. Chemistry
SECTION

4.
LOCATION

5. NINDB-85 (C)
SERIAL NO.

6. A Study of the Proteins of the Lens
PROJECT TITLE

7. Robert A. Resnik
PRINCIPAL INVESTIGATOR

8. Frank G. Suggs and Ann Wolff
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Many investigators have studied the proteins of the lens. These studies have not resulted in a clearly understood representation of what these proteins are chemically, and in fact different preparations are reported by different workers. Some reports have gone so far as to suggest that there are more than the four lens proteins which have been characterized by Morner in his classical studies. No detailed studies of the chemistry of these proteins have been published and only recently has there been an attempt at determining the molecular weight of one of these proteins.

Objective: The fractionation of the lens proteins into homogeneous components is the ultimate goal. Any one fraction that is obtained will be used for the determination of molecular weight and in dye binding studies. These data will be used to characterize the normal proteins.

Methods employed: Fractionation will be attempted by the use of a cellulose base ion exchange resin. The ultracentrifuge and electrophoresis will be used to determine homogeneity. Characterization of these proteins by comparison with other proteins will be carried out by the technic of equilibrium dialysis. These methods will be supplemented by any that will be particularly useful as the work progresses.

NINDB-85 (C)
SERIAL NO.

Major Findings: Preliminary attempts at fractionation with ammonium sulfate did not provide any homogeneous fractions as evidenced by a number of peaks in the sedimentation pattern. The ion exchange studies have not been started.

Significance to Institute Program: While much data are available on the size, shape, and electrical and chemical properties of other proteins, the data for lens proteins are rather skimpy and incomplete. Through studies, somewhat similar to those planned here, a better understanding of the roles of proteins has resulted in many instances. It seems desirable to carry out studies of this fundamental nature on lens proteins for this reason.

Proposed Course of Project: The ion exchange resin to be used and the necessary equipment is now available. The initial efforts will be aimed at separating, on a micro scale, proteins from rat lenses. The empirical procedure that is to be developed will be used on a larger scale for obtaining significant (or macro) quantities of one or more proteins. The comparison of normal and pathological proteins in addition to studying species differences will be included as a part of this project.

R.P.C.-3
Dec. 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-85 (C)
SERIAL NO.

11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1956								
FY 1957								

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICIAN ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 OR 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

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R.P.C. - 4
Dec. 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-85 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Ophthalmology
LABORATORY OR BRANCH

3. Ophth.Chemistry
SECTION

4.
LOCATION

5. NINDB-86 (C)
SERIAL NO.

6. The Chemistry of Alloxan
PROJECT TITLE

7. Robert A. Resnik
PRINCIPAL INVESTIGATOR

8. Ann Wolff
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

The lens of the eye contains proteins. It is reasonable to assume that clouding of this structure is a result of changes in these proteins. It is known that the optical properties of proteins may be altered in the process of denaturation. This often manifests itself by a change in the availability of free sulfhydryl groups of the protein. In instances of cataract formation the free sulfhydryl groups, present in protein and glutathione, are diminished in number. Such changes occur in experimental cataracts induced by alloxan. Although it is true in all probability that the ocular changes that result in diabetes mellitus and in alloxan diabetes are due to the diabetes itself, since the alloxan is known to oxidize sulfhydryl compounds, it is possible that, as a result, it could indirectly deplete the lens of this substance. Two suggestions have been proposed in an attempt to explain the toxic manifestations of alloxan: 1. Alloxan is toxic because it complexes with essential metals. 2. Alloxan is toxic because it reacts preferentially with the sulfhydryl groups of glutathione and protein.

Objectives: To study the reaction of alloxan with metals and sulfhydryl groups to determine whether these reactions might possibly be interpreted as having any relation to the toxicity of alloxan.

Methods Employed: One means of identifying substances is by comparison of their absorption spectra. The shape of the curve may be used as a qualitative means of identification, while the intensity of the spectrum may be used as a quantitative determination of the substance. In addition, any shift in the wavelength of the absorption maximum is indicative of a reaction taking place. In the case of reactions involving metals, complex formation is said to take place if a ligand (the complexing agent) reacts with a metal. These changes are also detectable by changes in the pH titration curve of the ligand when titrated in the presence and absence of metal.

Major Findings: Part 1. It has been proven that alloxan does not complex with metals as evidenced by experiments with copper. Alloxanic acid can and does complex with metals. This ligand is formed from alloxan by a base catalyzed rearrangement. Titrimetric and spectrophotometric evidence for this has been obtained.

Part 2. The reaction product between alloxan and glutathione has not been identified, but evidence has been obtained to obviate the possibility that the toxicity of alloxan can be attributed to the formation of a product with an absorption maximum at 305 mu. Substances with identical absorption spectra (or with a maximum at 305 mu) as the alloxan-glutathione adduct and which are not themselves known to be toxic have been studied. Thus violuric acid and the reaction product between dimethyl alloxan and glutathione absorb at 305 mu, but neither violuric acid nor dimethylalloxan are toxic.

The 305 chromophore has been proposed to contain the grouping, -N=C-C=O. A structure which is theoretically possible by analogy with the reaction of alloxan with free o-diamines has been proposed.

Significance to Institute Program: In the past, speculation without evidence has been made as to what the mechanism of the reaction of alloxan with physiological systems might be. This has been used by various groups in an attempt to explain the toxicity of alloxan. It has been established in this work that the toxicity of alloxan cannot be so explained. That is, it does not complex with metals and compound 305 may be obtained with the non-toxic, dimethylalloxan, and glutathione.

Proposed Course: Part 1. This is essentially complete. There are some aspects that are yet to be worked on but these involve some basic studies which will be deferred for the present. The nature of these future studies will be an analysis of the titration curves and an investigation of the effect of copper on the base catalyzed rearrangement of alloxan to alloxanic acid.

Part 2. This has not been completed. Studies involving reaction of N-substituted peptides with alloxan are contemplated.

R.P.C. - 3
Dec. 1955

Analysis of NIH Program Activities

BUDGET DATA SHEET

10. NINDB- 86 (C)
SERIAL NO.

11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1956								
FY 1957								

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICIAN ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1).

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Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB- 86 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

The Copper Complex of Alloxanic Acid. R.A.Resnik and H.Cecil, *Arch. Biochem. Biophys.*, (in press)

The Reaction of Alloxan with Glutathione and Protein. R.A.Resni and A.Wolff, submitted to Arch. Biochem. Biophys.

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

R.P.C. - 3
Dec. 1955

Analysis of NIH Program Activities

BUDGET DATA SHEET

10. NINDB- 86 (C)
SERIAL NO.

11. BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1956								
FY 1957								

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICIAN ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1).

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

R.P.C. - 4
Dec. 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB- 86 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

The Copper Complex of Alloxanic Acid. R.A.Resnik and H.Cecil, *Arch. Biochem. Biophys.*, (in press)

The Reaction of Alloxan with Glutathione and Protein. R.A.Resni and A.Wolff, submitted to Arch. Biochem. Biophys.

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Ophthalmology
LABORATORY OR BRANCH

3. Ophth.Chemistry
SECTION

4. ____________
LOCATION

5. NINDB-87 (C)
SERIAL NO.

6. The Effect of Sex Hormones on the Formation of Cataracts Induced by Galactose.
PROJECT TITLE

7. Robert A. Resnik
PRINCIPAL INVESTIGATOR

8. ____________
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

It has been well established that diets rich in galactose when fed to experimental animals result in the formation of cataracts. In addition, cataract formation occurs in infants and young children with idiopathic galactosemia. This condition, i.e. the formation of cataract, is peculiar to galactose of the hexoses. In the laboratory the susceptibility of rats to the effects of galactose seems to be confined to immature animals. Older animals appear to be refractory to the effects of galactose. In view of these observations it would appear desirable to determine the effect of castration on the metabolism of galactose.

Objectives: To determine whether the development of galactose induced cataracts is related to the sexual maturation of rats.

Methods Employed: Immature rats of both sexes are allowed to develop to maturity after castration is performed in the 4th to 6th week of age. The animals are then fed a 25% galactose diet and observed for the formation of cataracts. A group of controls of both sexes will be run in the same experiment.

Major Findings: This project was activated recently. No results are available as yet.

Significance to Institute Program: While it is known that diets high in galactose are able to produce cataracts in rats the reason for this effect is not known. In addition, why it is confined to the immature animals is not clearly understood. Information that might indicate some relationship between sexual maturation and the effect of galactose on the lens would be of interest both from the academic and practical points of view.

Proposed Course of Project: Until the results of the initial experiments are known the experiment as outlined in the section on methods will be used as such. It is contemplated to use very old animals in this experiment if possible.

R.P.C. - 3
Dec. 1955

Analysis of NIH Program Activities

BUDGET DATA SHEET

10. NINDB-87 (C)
SERIAL NO.

11.
BUDGET DATA

	ESTIMATED EXPENDITURES	BUDGETED POSITIONS			MAN YEARS			PATIENT DAYS
		PROF	OTHER	TOTAL	PROF	OTHER	TOTAL	
FY 1956								
FY 1957								

12. BUDGET ACTIVITY:

RESEARCH ☐ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICIAN ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1)

This work is being done with the assistance of Dr. Eugene Streicher of the Section on Aging, NINDB.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

R.P.C. - 4
Dec. 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB- 87 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Epidemiology
BRANCH

3. ______________________
SECTION

4. ____________
LOCATION

5. NINDB- 88 (C)
SERIAL NO.

6. Investigations of Amyotrophic Lateral Sclerosis: Epidemiologic,
PROJECT TITLE

Genetic, Clinical, Pathologic, and Therapeutic Studies

7. Leonard T. Kurland, M.D., Dr. P.H.
PRINCIPAL INVESTIGATOR

8. Clinical and Therapeutic--Donald W. Mulder, M.D., Consultant in
OTHER INVESTIGATORS

Neurology, Mayo Clinic

Chamorro Studies--Lorenzo L. G. Iriarte, now a student at the Johns Hopkins School of Hygiene and Public Health, returning to Guam this June, 1956 to continue the work in ALS on Guam.

--Jose Torres, now a medical student at the Georgetown University School of Medicine. The study of Chamorros living in California will be continued during the summer months of 1956.

Pathological Anatomy--George Sayre, M.D., Section of Pathology, Mayo

Nutritional Studies--Mrs. Marjorie Grant Whiting, Department of Nutrition, Harvard School of Public Health

9. PROJECT DESCRIPTION

Some of the studies listed in the project description sheet of last year are still in progress. Several have been completed and have been reported or will be reported in the near future.

Objective: To review and clarify aspects of motor neurone disease (amyotrophic lateral sclerosis and its clinical components - progressive muscular atrophy and progressive bulbar palsy) and determine the reason for the unusual prevalence in the Mariana Islands.

9. PROJECT DESCRIPTION (Continued)

Method employed: An unusual opportunity to investigate the problem has been afforded by the extremely high prevalence of ALS among the Chamorros (natives) of Guam and the other Mariana Islands in the Western Pacific. Unusual or suspicious findings would be investigated more thoroughly at the Clinical Center.

a. Clinical description of patients on Guam and at the Mayo Clinic, with an analysis of the principal clinical features, is still under way. An investigation was carried on at the Mayo Clinic to determine if any variation in gastric cytology by chymotrypsin lavage could be detected.

b. Clinical Pathology: The clinical pathology program described last year has been temporarily discontinued because of lack of personnel available for this study on Guam. Through this program various blood and spinal fluid biochemical studies and genetic typing were to be conducted.

c. Pathological Anatomy: Review of series of ALS cases at the Armed Forces Institute of Pathology under the supervision of Dr. Webb Haymaker.

Material collected in Guam and from Mayo Clinic patients is also being examined by Dr. Sayre. Particular interest in the United States group is centered on those patients with a positive family history of motor neurone disease.

d. Epidemiology and Genetics: In California, a comparison of the incidence of ALS of Chamorros now living in that state and their families still in Guam is being carried out.

Comparisons of familial incidence among patients and a random sample "control" group on Guam are still being determined. In these latter groups a comparison of possible environmental etiologic factors is being investigated.

Studies of nutritional status are being conducted by Mrs. Whiting among Chamorros here in this country as well as on Guam and other Mariana Islands.

A search was made of records in the Archivo de Indias in Seville and the Government Archives in Madrid (Spain) and in the Vatican Library in Rome (Italy) to determine if ALS was present in the Mariana Islands prior to the arrival of the Spanish or was introduced after the Spanish arrived in the islands. This information would help determine how important it was to search for a possible exogenous factor.

9. PROJECT DESCRIPTION (Continued)

e. Therapeutic Studies: A number of possible agents are being tested among the patients on Guam and have been tested on a series of patients observed at the Mayo Clinic.

Major findings: Amyotrophic lateral sclerosis appears to have become highly prevalent in the Mariana Islands after the arrival of the Spanish explorers about 1670. Amyotrophic lateral sclerosis, on Guam, which is clinically and pathologically identical with the disease as we know it elsewhere, does not appear to be affected by pregnancy and presumably does not affect the course of pregnancy. No unusual blood groupings, biochemical observations, or therapeutic results can be reported for the population of Guam. The gastric cytology study at the Mayo Clinic was unsuccessful and will be repeated. Electromyographis results in the Guam area are similar to those observed among ALS patients elsewhere.

Although the study is incomplete, there are findings which suggest that the prevalence of ALS is high among Chamorros residing in California.

A review of the reported findings of Ask-Upmark of Uppsala, Sweden, in "Amyotrophic Lateral Sclerosis Observed in Five Persons After Gastric Resection" was made and it is my impression that Ask-Upmark's description of a correlation of ALS and gastrectomy was not quite so. After careful examination of the case records in his laboratory, there was some question regarding the diagnosis in several patients. Since gastrectomy had been performed on over 1,000 patients in the series he studied, the few cases in which ALS developed could be a chance happening. This would tend to de-emphasize the importance of gastrectomy or gastric malformation in the etiology of ALS.

Significance to neurological research: In addition to providing clinical data for an important disease of the nervous system, the study illustrates the value of combined field epidemiologic and clinical approach.

Clarification of the etiology of the disorder would be expected to improve the opportunity for therapeutic success.

Proposed course of the project: No change. Several of the above projects are still under way. The study in California will be continued in the summer of 1956.

R.P.C. 2
Dec. 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB- 88 (C)
SERIAL NO.

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11. BUDGET DATA

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12. BUDGET ACTIVITY: Research

13. U. S. Navy, Bureau of Medicine and Surgery, U. S. Naval Hospital on Guam

Government of Guam: Department of Medical Services

Mayo Clinic

14. None

R.P.C. 3
Dec. 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications

15. NINDB- 88 (C)
SERIAL NO.

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16. PUBLICATIONS FROM THIS PROJECT DURING 1955:

Kurland, L. T. and Mulder, D. W. Epidemiologic Investigations of Amyotrophic Lateral Sclerosis. 2. Familial Aggregations Indicative of Dominant Inheritance. Neurology, 5 (Nos. 3 and 4): 182-196; 249-268, March-April, 1955.

Kurland, L. T., Mulder, D. W., and Westlund, K. D. Multiple Sclerosis and Amyotrophic Lateral Sclerosis: Etiologic Significance of Recent Epidemiologic and Genetic Studies. New England Journal of Medicine, 252:649-653, 697-702 (April 21 and 28), 1955.

Huston, Cdr. J. Wilson (MC), USN, Lingenfelder, J., Mulder, D. W. and Kurland, L. T. Pregnancy complicated by Amyotrophic Lateral Sclerosis. (To be published in the American Journal of Obstetrics and Gynecology).

Kurland, L. T. and Mulder, D. W. Scientific Exhibit "Epidemiological Investigations of Amyotrophic Lateral Sclerosis" (To be published in Archives of Neurology and Psychiatry).

Kurland, L. T. and Mulder, D. W. Motion Picture (sound, 16 mm.) - Amyotrophic Lateral Sclerosis in the Mariana Islands.

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17. HONORS AND AWARDS TO PERSONNEL DURING 1955: None

R.P.C. 1
Dec. 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Epidemiology
BRANCH

3. ______
SECTION

4. ______
LOCATION

5. NINDB - 89 (C)
SERIAL NO.

6. Epidemiologic Surveys of Selected Neurologic and Ophthalmologic Disorders
PROJECT TITLE

7. Leonard T. Kurland, M. D., Dr. P. H.
PRINCIPAL INVESTIGATOR

8. Joseph Berkson, M. D., Division of Biometry and Medical Statistics,
OTHER INVESTIGATORS

Mayo Clinic

Robert G. Taub, M. D., formerly a Fellow at the Mayo Clinic, in

Ophthalmology; now practicing ophthalmology in Chicago, Illinois.

9. PROJECT DESCRIPTION

The number of diagnosed cases and the incidence and prevalence rates for selected neurological disorders among the resident population of Rochester, Minnesota, from 1945-54, inclusive, is being carried out through an analysis of the records at the Mayo Clinic. The list of disorders includes cerebral palsy, epilepsy, demyelinating disorders, amyotrophic lateral sclerosis, Parkinsonism, brain and spinal cord tumors, etc. (also glaucoma)

The purpose of the study is to test the methods which have been developed and which are to be employed in the larger cities and to determine which of the disorders included are suitable for population survey techniques. Rates and ratios determined in this community will not only aid in planning the work load in the larger communities but will, in spite of the small population in Rochester, Minnesota, often be of value themselves in estimating incidence and prevalence of some of the disorders which have been studied. The combination of these morbidity survey data and mortality statistics being obtained from the United States and the Canadian Offices of Vital Statistics are expected to provide the most accurate data on the frequency and geographic distribution of these disorders available to date.

The detailed report of the Rochester, Minnesota, study has been completed; its condensation and publication have been temporarily delayed.

R.P.C. 2
Dec. 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB - 89 (C)
SERIAL NO.

11.

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12. BUDGET ACTIVITY: Research

13. Mayo Clinic

National Office of Vital Statistics, U. S. P. H. S.

Office of Vital Statistics, Canada

14. None

Honors, Awards, and Publications

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16. PUBLICATIONS FROM THIS PROJECT DURING 1955: None

17. HONORS AND AWARDS TO PERSONNEL DURING 1955: None

BRANCH OF ELECTROENCEPHALOGRAPHY

The activity of the Branch has substantially increased during 1955.

EEG examinations for routine diagnosis and for research show a 60% increase over those performed in the previous year.

A total of 1276 examinations were carried out on patients referred to the Branch from our Institute and from other Institutes as follows:

N.I.N.D.B.	1065
N. C. I.	123
N. H. I.	30
N.I.A.M.D.	29
N. M. I.	27
N.I.M.H.	2
Total	1276

Of the above total, 232 examinations were performed on out patients.

Electrocorticographic studies during surgical exposure of the cerebral cortex were performed on 38 epileptic patients.

The major research project in the clinical field remains the study of the physiopathology of the epilepsies with particular emphasis on the group of focal lesions within the temporal lobe. This project was described in detail in the last yearly report. It was stated that this is a long range project and the necessity for collecting a large number of patients was emphasized, together with the need for a careful and long follow-up of operated subjects before drawing any definite conclusion.

The second project is a corollary of the preceding one. It deals with the diagnosis and classification of the various types of epileptics by means of activation procedures. It has been found that the slow injection of Metrazol, carried up to the point of eliciting a clinical seizure, yields a wealth of electrographic and clinical information which, when properly interpreted, proves to be extremely useful in clarifying the diagnosis. Interesting observations on the electrographic correlates of numerous clinical signs could also be made during this study.

A third project is still under way also in the field of the epilepsies (anti-convulsant therapy). It concerns the EEG evaluation of possible effects of new types of medicaments, and it is carried out in collaboration with the Section of Neurochemistry.

The question of seizures in cases of cerebral palsy and the possibility of their surgical treatment is the object of another project. The outline of the electrographic criteria for the classification of these rather complex clinical cases is the chief aim of our study.

A new project has been recently started in collaboration with the N.I.M.H. and the Institute of Living (Hartford, Conn.). It concerns the study of old age changes in the brain and in particular, the relationship between the cerebral blood flow and electroencephalographic changes.

The experimental research in animals deals with the thalamo-cortical relationship and with the problem of spread of epileptic discharges. The subject of one project is the study of the "recruiting response" in cortical and subcortical structures, while another project deals with the mechanism of "spindles" which characterize the electrical activity of the brain in certain experimental conditions.

In the field of experimentally induced epileptogenic lesions two projects are under way. The purpose of these studies is to gain further information on the different electrographic behavior in cases where the lesion is produced at a subcortical level on one hand, and in those in which the lesion is located in various cortical regions, on the other.

Preliminary results of three of the above-described projects were presented in the course of this year at different Scientific meetings.

During the past year the staff of the Branch of Electroencephalography has been increased and includes at the present time three EEG technicians and one technician in experimental neurology. In addition, a research associate has joined our Branch during the last six months, collaborating very actively on several of the projects.

R.P.C. 1
December 1955

Analysis of NIH Program Activitives

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Electroencephalography
LABORATORY OR BRANCH

3.
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NINDB-90 (C)
SERIAL NO.

6. Electrographic (EEG and ECoG) study of temporal lobe epilepsy.
PROJECT TITLE

7. C. Ajmone Marsan
PRINCIPAL INVESTIGATOR

8. Maitland Baldwin
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The two main objectives of this project are: a) to gain more information on the physiopathology underlying this particular form of epilepsy; b) to establish reliable criteria in the electroencephalographic diagnosis of this disorder. In considering the surgical treatment of this form of epilepsy, the selection of patients becomes of paramount importance and the EEG findings are almost always those upon which this selection is based. In recent years considerable material has been accumulated in this field, yet we are still unable to answer a number of important questions, among which:
a) is the epileptogenic lesion cortical (i.e., susceptible to surgery) or subcortical (i.e., non-operable?) What are the EEG criteria to differentiate the two forms?
b) Why some forms of temporal abnormalities can be activated during sleep while others are unaffected or decreased?
c) Why apparently similar clinical seizures have rather different electrographic correlates?
d) What are the relations between parasagittal region and temporal lobe?

Methods employed and patient material: This main project is, therefore, subdivided into the following sub-sections:

A) EEG diagnosis of temporal lobe epilepsy.
B) Electrocorticographic study of temporal lobe discharges.
C) Electrographic-clinical correlations of epileptic seizures.
D) Sleep and temporal lobe epilepsy.
E) Electrographic manifestations of subcortical epileptogenic lesion.
F) Clinical-pathological correlations in cases with parasagittal and temporal EEG abnormalities.
G) Cortical physiology in man (electrocorticographic study of spontaneous, evoked, and abnormal activity with particular emphasis on the temporal region).

Routine EEG examinations are carried out on all epileptic patients admitted by the Neurosurgical Branch. Numerous tracings are obtained in various conditions (after withdrawal of medication, during induced sleep, during spontaneous or induced seizures) using a minimum of 21 electrodes and various methods of localization. If the patient is eventually selected for surgical treatment, the electrical activity will be recorded from its exposed cortex both at rest and following electrical stimulation of various cortical and subcortical structures, before and after surgical ablation of the abnormal tissue. EEGs are then taken at regular intervals in the post-operative period.

Major findings: This is a long range project in which positive and useful results can only be obtained with a large number of cases and with pathological and clinical correlations. The clinical evaluation of surgical treatment of epilepsy requires a minimum of one to three years follow-up and most of the conclusions in regard to electroencephalographic criteria for physiopathology and diagnosis will obviously depend upon the surgical results. This limitation applies particularly to the sub-sections A, D, E, F, and partly to sub-sections B and C. Interesting observations were however made (sub-sections B and G) on the electrical activity of the exposed insula where epileptiform discharges can often be recorded. The behavior of paroxysmal abnormalities following cortical undercutting, and their relation with electrically induced afterdischarge was also investigated. The effect of arousal, acoustic stimulation and speech upon the spontaneous activity of various regions of the temporal cortex was studied.

Significance to the program of the Institute: The main program of the Neurosurgical Branch of the NINDB concerns the temporal lobe epilepsy. This particular research project of our Branch is a primary adjunct to the research of the Neurosurgical Branch.

Proposed course of project: Fundamentally unchanged.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB-90 (C)
SERIAL NO.

12. BUDGET ACTIVITY: Research

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1756: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM I)

Branch of Neurological Surgery - NINDB

Honors, Awards, and Publications

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

None

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Electroencephalography
LABORATORY OR BRANCH

3.
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NINDB-91 (C)
SERIAL NO.

6. Metrazol-induced seizures - Clinico-electrographic correlations in cases of focal epilepsy.
PROJECT TITLE

7. C. Ajmoné Marsan
PRINCIPAL INVESTIGATOR

8. B. Ralston
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: a) to determine the validity of Metrazol activation, b) to establish criteria of localization and lateralization of an epileptogenic lesion, c) to obtain further and more precise information on the electrographic correlates of the various clinical manifestations occurring during a seizure.

Methods employed and patient material: Metrazol activation (slow i.v. injections according to the method of Jasper and Courtois 1953) was carried out in over 100 patients admitted by the Neurosurgical branch. The administration of the drug is continued until a clinical seizure is induced. Objective and subjective signs are carefully recorded and correlated with the EEG changes throughout the entire procedure.

Major findings: The following information was obtained by the study of Metrazol-induced seizures (MIS).

a) The MIS faithfully reproduces the patient's attack pattern (while on medication) in 85% of the cases and in over 90% the spontaneous attacks observed while off medication and at the time of the Metrazol activation. In only 4% was the MIS wholly unlike the habitual patient's attack.

b) The average amount of Metrazol for a MIS is 6.55 mgs/Kg ± 3.26. There is no correlation between threshold value and age, sex, or frequency of attacks. There is a slight correlation between threshold and duration of seizures in years and between threshold and type of epilepsy. The chances for the MIS to be a major generalized convulsion and/or an aspecific attack are not necessarily increased by increasing the dose of Metrazol.

c) The value and reliability of various clinical lateralizing signs occurring in a MIS could be established. Aphasia and arm and leg movements are the most while eyes turning the less reliable signs.

d) Motor lateralizing signs are present in an unexpectedly high number of temporal cases while visceral or non-visceral automatisms can be observed occasionally in cases with a parasagittal lesion. Aphasia predominates in bitemporal lesions. Consciousness may be completely unimpaired in a high percentage of seizures originating from the parasagittal region. The incidence of major generalized attacks markedly increases from unitemporal, to bitemporal to parasagittal to centrencephalic epilepsy.

e) Cases of temporal lobe epilepsy.
i) If the MIS consists of automatism alone, the EEG is strikingly characterized by lack of changes or by unitemporal activation. ii) If there is automatism plus aphasia the EEG changes are usually bilateral temporal. iii) If there is automatism plus local motor phenomena, the EEG changes are focal or bilateral temporal (if the same clinical pattern takes place with no EEG changes, the lesion could be in the parasagittal area). iv) If there is automatism plus local motor sign and a major seizure the EEG pattern may vary but there is a preponderance of bitemporal changes. v) Automatisms plus major seizures always are accompanied by EEG changes which can be focal temporal or diffuse.

f) Other similar correlations were made for MIS in non-temporal epileptogenic lesions.

g) The various data obtained during MIS in well-established clinical cases could be satisfactorily applied to a number of cases in which the clinical-EEG diagnosis and classification was uncertain or not established, and valuable information was obtained in a high percentage of cases.

h) Comparison of the results obtained by the study of a MIS and by the study of only the early paroxysmal changes elicitable with Metrazol indicates the superiority of the former which yields a substantially higher number of useful results.

Significance to the program of the Institute: See project 1.

Proposed course of project: Collect a larger number of activations within the next year. Compare the effect of various activations in the same patient and study the modifications of the seizure pattern and of the EEG before and after surgical treatment.

A more accurate study of the electrical activity of various cortical regions will eventually be achieved by using a 16 channel electroencephalograph.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-91 (C)
SERIAL NO.

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11. BUDGET DATA:

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12. BUDGET ACTIVITY:

RESEARCH /x/ ADMINISTRATION /_/

REVIEW & APPROVAL /_/ TECHNICAL ASSISTANCE /_/

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13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM I)

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

R.P.C. - 3
December 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-91 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

None

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Electroencephalography
LABORATORY OR BRANCH

3.
SECTION

4. Bethesda and Hartford, Conn.
LOCATION (IF OTHER THAN BETHESDA)

5. NINDB-92 (C)
SERIAL NO.

6. Electroencephalographic study and cerebral blood flow in old age.
PROJECT TITLE

7. W. D. Obrist
PRINCIPAL INVESTIGATOR

8. C. Ajmone Marsan, J. Birren et al
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To study the correlations between the EEG pattern observed in old (normal) subjects and their cerebral blood flow.

Methods employed and patient material: Subjects are provided by the NIMH. Routine EEG examination is carried out and in addition, tape recording for use in electronic frequency analysis. All tape recordings are obtained from bipolar runs involving three areas: fronto-central, middle-posterior temporal and parieto-occipital.

Proposed course of the project: This project was started recently and will be carried out throughout the coming year.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-92 (C)
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM I)

NIMH and Institute of Living, Hartford, Conn.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

R.P.C. - 3
December 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-92 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

None

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

None

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Electroencephalography
LABORATORY OR BRANCH

3.
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NINDB-93 (C)
SERIAL NO.

6. Electrographic study in cases of cerebral palsy with seizures
PROJECT TITLE

7. C. Ajmone Marsan
PRINCIPAL INVESTIGATOR

8. M. Baldwin, A. Dekaban, G. Millichap
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To establish diagnostic and prognostic criteria in regard to the outcome of seizures in case of massive cerebral lesions when medical treatment has failed and the patient is a possible candidate for surgery.

Methods employed and patient material: Serial EEG examinations are carried out on patients admitted by the branch of Neurological surgery. The electrographic study is performed in different conditions and with various activating procedures. Particular emphasis is placed on localizing devices and in differentiating cortical from sub-cortical lesions. In cases of surgical operation, the exposure of an entire hemisphere provides unparalleled opportunities for electrical exploration of various cortical areas and of a number of subcortical structures.

Major findings: A limited number of patients have been studied in this relatively recent project. A long clinical and electrographic follow-up are needed in order to assess the validity of any offered interpretation.

Significance to the program of the Institute: This project is an important complement to similar researches for the coming year in the section of Neuropathology and in the Branch of Neurological Surgery of the NINDB.

Proposed course of the project: Accumulate wider information through a larger number of patients with a longer post-operative follow-up. At least 2-3 years project period.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data

10. NINDB-93(C)
SERIAL NO.

12. BUDGET ACTIVITY: Research

Honors, Awards, and Publications

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

Problems in the EEG Analysis of Epileptic Activity in Patients with Massive Cerebral Lesions. - C. Ajmone Marsan and M. Baldwin, EPILEPSIA - in press

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

None

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description

1. Neurological Diseases and Blindness
INSTITUTE

2. Electroencephalography
LABORATORY OR BRANCH

3. ______
SECTION

4. ______
LOCATION (IF OTHER THAN BETHESDA)

5. NINDB-94(C)
SERIAL NO.

6. Electroencephalographic control of anticonvulsant therapy.
PROJECT TITLE

7. C. Ajmone Marsan and D. Tower
PRINCIPAL INVESTIGATORS

8. C. E. Wells
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives and patient material: These are extensively described in project NINDB-12(C). The EEG picture is emphasized in this part of our project. Each patient receives a series of EEG examinations before the beginning of the treatment in order to evaluate the type and amount of paroxysmal abnormalities. Following the beginning of medication, the patient is re-examined approximately once a week for various months.

Major findings: The results of this study are still to be evaluated. The preliminary impression is that the clinical improvement is not paralleled by a similar electrographic improvement, and on the whole, most of the patients who seem to do well clinically still show an abnormal tracing where the paroxysmal discharges are still present with characters similar to those observed in the pre-medication records. It must be noted, however, that - at least electrographically - the selection of patients for this study was made on the basis of very abnormal records.

Significance to the program of the Institute: The possibility of determining with objective criteria the effect of an anticonvulsant treatment presents obvious advantages. The persistance of an abnormal tracing in cases of definite clinical improvement makes the prognosis more guarded than in cases of full normalization of the EEG accompanying the clinical improvement. Possibly only certain types of EEG abnormalities are susceptible to improvement and consequently only certain types of cerebral seizures can definitely benefit from the treatment under study, even though some transitory diminution in the number of seizures may be observed in a relatively high percentage of cases.

Proposed course of the project: To elaborate the various EEG findings, from a quantitative and, possibly, qualitative, standpoint and to correlate them with the clinical ones of project NINDB 12(C).

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data

12. BUDGET ACTIVITY: Research

Honors, Awards and Publications

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

None

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Electroencephalography
LABORATORY OR BRANCH

3. ______
SECTION

4. ______
LOCATION (IF OTHER THAN BETHESDA)

5. NINDB-95 (C)
SERIAL NO.

6. Recruiting response in cortical and subcortical structures.
PROJECT TITLE

7. C. Ajmone Marsan
PRINCIPAL INVESTIGATOR

8. ______
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: Further investigation on the function of the non-specific system of the thalamus.

Methods employed: The experiments are carried out on cats under nembutal anesthesia. Electrical stimulation of subcortical structures is performed by means of steel electrodes inserted and held in place by a stereotaxic instrument. The square pulses of various duration, voltage and frequency are obtained from two Grass stimulators in order to evaluate the inter-relation between two different structures stimulated at variable delay. Cortical and subcortical recordings are made with oscilloscopic and ink-writing techniques with standard apparatuses (Dumont CRO; Offner EEG; Grass pre-amplif.)

Major findings: Very often the recruiting response not only consists of a series of potentials waxing and waning in their amplitude but these potentials also show a rhythmical variation in latency which undergoes substantial changes in value when measured in the "waxing" or in the "waning" phase. At times there is a definite relation between increasing in amplitude and shortening of the latency while at other times, the latency tends to become progressively longer only in the waning phase while remaining relatively short at the beginning of the recruiting when the amplitude of the response is not yet fully developed. It is postulated that the recruiting phenomenon may occur following excitation of shorter or longer pathways. The longest paths (those with a larger number of synapses) can be supposed to have (those with a larger number of synapses) can be supposed to have a more restricted field of distribution but to be very effective within this limited field. Shorter paths may excite a larger number of cells but in order to do this they require considerable temporal summation. The "recruiting" would, therefore, depend upon a progressive activation of two main groups of elements differing from each other by the number of synapses involved and the "waning" phase could be due to dropping out of the neurons excited by the shortest paths.

When recording the non-specific response from a surface-cortical electrode and from a needle electrode placed at different levels within the cortex itself, the underlying white matter, radiations, various basal ganglia and eventually the thalamus, not only the latency tends to remain the same, but recruiting and waxing and waning do occur in structures where obviously no cortical neurons are involved, and also after these have been depressed (cortical cocainization) or eliminated (cortical ablation). It logically follows that all of these events must originate subcortically and probably within the thalamus itself.

The transformation of polarity undergone by the response in the depth, its relatively unchanged amplitude and some of the mentioned observations can be explained by postulating the presence of two interrelated but separated electrical fields, one originating from fibers (positive deflection) the second from cell activity, a situation somewhat similar to that visualized by Grey Walter (1953). Thus, the transition from a high amplitude negative, to a lower amplitude negative-positive, to a high amplitude positive deflection throughout the cortex and underlying white matter can be interpreted as the result of the algebraic sum of two waves of opposite polarity with predominance of either one above or below a certain level; this level would not signify the passage from "sink" to "source" but the borderline between the two fields.

Significance to the program of the Institute: The system under investigation seems to be involved in certain types of epileptic disorders. A deeper knowledge of its physiology could probably throw some light on the complex mechanisms underlying psychoparetic manifestations, alterations of awareness and attention commonly found in epileptics.

Proposed course of project: Continue the investigation of this system with particular reference to a) inter-relationship with specific system, b) effect of CNS stimulants.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-95 (C)
SERIAL NO.

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11. BUDGET DATA:

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12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM I)

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH)

R.P.C. - 3
December 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-95 (C)
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

None

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Electroencephalograph
LABORATORY OR BRANCH

3.
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NINDB-96 (C)
SERIAL NO.

6. Spindle mechanism and experimental epileptic lesions.
PROJECT TITLE

7. B. Ralston
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To study the possible role of the spindling mechanism in the transmission of focal epileptic discharges.

Methods employed: Creation of acute epileptic foci by the use of Penicillin in various cortical and subcortical regions and the changing of the transmission from these foci to other areas by the effect on the spindle formation. Experimental animals - cat.

Major findings: Foci produced in certain areas such as the mesial thalamus and the cingulate gyrus have an activating effect on the spindle formation and also synchronize these discharges over wide cortical areas. There is also an alteration in the frequency of the spindling to a pathological degree.

Significance of the Program to the Institute: It is possible that the discharges of so-called centrencephalic and subcortical epilepsy are the result of focal lesions "broadcasting" via this mechanism.

Proposed course of project: To continue and extend these observations on the cat and to make additional ones on the monkey, and to study the effects of various anesthetic and other pharmacological agents on the spindle formations.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-96 (C)
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	TECHNICAL ASSISTANCE	☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM I)

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R.P.C. - 3
December 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-96 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

None

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

None

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Electroencephalography
LABORATORY OR BRANCH

3.
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NINDB-97 (C)
SERIAL NO.

6. Experimental epilepsy - Electrographic studies in cortical and subcortical epileptogenic lesions.
PROJECT TITLE

7. B. Ralston
PRINCIPAL INVESTIGATOR

8. C. Ajmone Marsan
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The purpose of this project is to study the behavior and distribution of paroxysmal discharges originating from various cortical regions on the one hand, and from various thalamic nuclei on the other.

Methods employed and patient material: Acute experiments on cats under various anesthetics. Lesions produced with Penicillin and/or Alumina Cream introduced by means of a stereotaxically oriented needle. Cortical and subcortical recording with an 8 channel Offner electroencephalograph and a dual beam CRO.

Major findings: Interesting observations have been made to date on the general pattern of the induced epileptiform activity which seems to have particular features depending on the various locations within the cortex and the subcortical structures. Preferential pathways of projection have been established for the epileptiform discharges within one hemisphere, between the two hemispheres and between thalamus and cortex.

Significance to the program of the Institute: One of the main clinical projects is the EEG study of focal (temporal in particular) epilepsy. The possibility of establishing criteria for selecting cases with cortical from those with subcortical lesions would be of the greatest significance and practical use.

Proposed course of project: Continue the study and extend it to monkey with particular emphasis upon the cingulate, supplementary motor and temporal areas.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-97 (C)
SERIAL NO.

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11. BUDGET DATA:

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12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

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13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM I)

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R.P.C. - 3
December 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-97 (C)
SERIAL NO.

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16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

None

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

None

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Electroencephalography
LABORATORY OR BRANCH

3.
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NINDB-98 (C)
SERIAL NO.

6. Metrazol and sleep activation in experimental epilepsy
PROJECT TITLE

7. B. Ralston
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION (see projects 2 and 8 of the EEG Branch).

Objectives: The application of these two methods of activation in cases of experimentally produced epileptogenic lesions provides further information on the mechanism of seizures and afford the possibility of better differentiation between cortical and subcortical lesions.

Methods employed and material:

See projects 2 and 8 of the EEG Branch.

Major findings: The material obtained in more than 40 cats has still to be elaborated.

Significance to the program of the Institute:

See projects 2 and 8 of the EEG Branch.

Proposed course of project: Complete this study and correlate with results on epileptic patients.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-98 (C)
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐
REVIEW & APPROVAL ☐ TECHNICAL ASSISTANCE ☐

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM I)

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R.P.C. - 3
December 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-98 (C)
SERIAL NO.

---

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

None

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17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

None

Annual Report of the Basic Research Program, NIMH-NINDB

January 1 to December 31, 1955

It is difficult to separate fundamental research in neurological disease from that in mental illness; for that reason a combined Basic Research Program was initiated in 1951 under a single Scientific Director, supported by both the National Institute of Mental Health and the National Institute of Neurological Diseases and Blindness. This program is based upon the thesis that progress in the diagnosis and treatment of nervous and mental diseases rests firmly upon a basic understanding of the nervous system through the biological and behavioral sciences. In contradistinction to other areas of medical research, most neurological and psychiatric disorders are of unknown etiology at the present time. The crucial questions in these disorders have not been answered. In many areas they have not even been phrased. For this reason, in addition to research attacks upon specific disease entities, which is the special problem of the programs in Clinical Investigation, there has been a conscious effort to establish a comprehensive program with adequate support in each of the principal scientific disciplines. In addition, research on many unsolved problems is conducted in the relatively neglected areas between the disciplines. A most important aspect of the intramural program is its ability to bring together individuals with the experiences, techniques, and attitudes of the various basic disciplines along with clinical investigators so that each new idea or finding may have the benefit of examination, criticism, and exploitation in all of its ramifications.

The year 1955 saw the culmination of the organizational phase of this program. Even the newest laboratories have seen a full year of established and fruitful activity. This activity encompasses the complete spectrum of fundamental research relevant to mental and nervous diseases ranging from the anatomical sciences to socio-environmental studies. In Table I the various research undertakings are classified in terms of the areas of fundamental knowledge which they are designed to elucidate.

It is of interest to classify these same research projects in terms of the important clinical problems or disease entities to which they are relevant. This can be at best a gross underestimate since it is a commonplace observation that the ultimate significance of fundamental knowledge is considerably greater than the specific questions which it answers. Table II represents one attempt to indicate at least some of the clear and demonstrable relationships.

TABLE I - Fundamental Research Problems of the Basic Program, NIMH-NINDB

STRUCTURE

Development of the nervous system: NINDB-3, 6, 17, 18

Growth and regeneration: NINDB-1, 2, 5, 7, 16, 17, 18

The anatomy of sensory systems: NINDB-28, 29

Cytology and cytochemistry: NIMH-60, NINDB-4, 12, 13, 15, 19, 22, 24, 25

Functional neuroanatomy: NINDB-26, 27, 28, 29

Experimental pathology: NIMH-33, 34, 35, 37, 38, NINDB-20, 23

Genetics: NIMH-17, 92

FUNCTION

The nature of the nerve impulse: NIMH-5, 6, 7, 18, NINDB-37, 38, 39, 45, 48, 49, 50, 52, 53

Interactions between neurons: NIMH-1, 2, 4, NINDB-54, 55

Spinal cord physiology: NINDB-5, 21, 31, 54, 55

Physiology of the brain stem: NIMH-1, 2, 10, 21, 50, 51, 55, NINDB-11, 30, 32, 33

Physiology of the cerebral cortex: NIMH-3, 4, 8, 9, 50, 51, 55, 56

Sensory physiology: NIMH-54, 55, 65, 67, NINDB-18, 51

METABOLISM

Chemical structure: NIMH-12, 13, 14, 15, 16, 17, 19, 33, 34, 63, NINDB-13, 14, 24, 25

Energy transformations: NIMH-3, 20, 21, 22, 62, NINDB-40, 53

Synthesis: NIMH-12, NINDB-40, 41, 42, 44, 46

Intermediary metabolism: NIMH-24, 25, 29, 30

Cerebral circulation and nutrition: NIMH-20, 21, 22, NINDB-20, 23, 35

THE ACTION OF DRUGS AND HORMONES

Mechanism of drug action: NIMH-1, 7, 20, 21, 36, 44, 46, 47, 48, 49, 65, 71, NINDB-8, 22, 39, 43, 47

Hormone synthesis: NIMH-24, 26, 27, 30, 32

Hormone action: NIMH-25, 36, 49, NINDB-19, 33, 34, 36

Drug metabolism: NIMH-24, 26, 27, 39, 41, 42, 43, 48, 61

BEHAVIORAL SCIENCES

Anatomical, physiological, and chemical correlates of behavior: NIMH-9, 10, 11, 20, 21, 32, 40, 41, 45, 50, 51, 53, 54, 56, 57, 64, NINDB-3, 9

Aging: NIMH-20, 58, 59, 60, 61, 62, 63, 64, 81, NINDB-4

Learning: NIMH-64, 71, 72, NINDB-9, 10, 11

Perception: NIMH-54, 55, 58, 59, 65, 66, 67, 71

SOCIO-ENVIRONMENTAL

Population dynamics: NIMH-68, 69, 70

Adaptation of the family to stress: NIMH-73, 74, 75, 76, 83

Epidemiology of mental disorders: NIMH-77, 78, 86

Sociological studies of therapy: NIMH-79, 80, 82, 85, 87

Human interactions: NIMH-88, 89, 90, 91

TABLE II - The Relevance of Basic Research Projects to Clinical Problems and Diseases

Diagnosis:
NIMH-9, 53
NINDB-27

Pharmacotherapy:
NIMH-1, 7, 21, 24, 26, 27, 36, 40, 41, 42, 46, 47, 61, 65, 71, 20
NINDB-8, 47

Psychoses:
NIMH-1, 9, 10, 11, 12, 17, 20, 24, 26, 27, 31, 36, 40, 41, 46, 50, 52, 57, 65, 66, 67, 68, 70, 72, 73, 74, 75, 76, 77, 79, 80, 85, 86, 87, 88, 89
NINDB-15, 43

Psychosomatic Diseases:
NIMH-10, 20, 24, 32, 50
NINDB-9, 10, 11, 17, 19, 34, 36

Aging:
NIMH-13, 20, 53, 58, 59, 60, 61, 62, 63, 64, 81
NINDB-4, 7

Mental Retardation:
NIMH-12, 13, 16, 17, 19, 23, 25, 29, 30, 50, 51, 53, 56, 66, 71, 92
NINDB-3, 6, 9, 10, 13, 15, 22, 42, 44, 46

Juvenile Delinquency:
NIMH-50, 52, 68, 69, 72, 78, 82, 86, 88, 89, 90, 91, 93

Drug Addiction:
NIMH-39, 42, 43, 44, 45, 46, 47, 48, 49

Psychoneuroses:
NIMH-10, 20, 32, 50, 67, 68

Neuromuscular Diseases:
NIMH-3, 15, 16, 93
NINDB-8, 16, 27, 50, 54, 55

Trauma and Disease of Peripheral Nerves:
NIMH-5, 6, 14, 18, 26, 93
NINDB-16, 37, 38, 39, 45, 48, 49, 52, 53

Sensory Diseases:
NIMH-2, 54, 55, 58, 59, 65, 66, 67, 71, 72
NINDB-18, 28, 29, 51

Cerebral Palsy:
NIMH-8, 9, 15, 16, 53, 92
NINDB-3, 6, 7, 8, 13, 15, 18, 22, 24, 25, 26, 42, 44, 46

Cerebrovascular Diseases:
NIMH-14, 20, 21, 22, 93
NINDB-17, 19, 20, 23, 35

Multiple Sclerosis:
NIMH-33, 34, 35, 37, 38
NINDB-15, 27, 40, 41, 42, 44, 46, 54, 55

Epilepsy:
NIMH-3, 8, 21, 22, 93
NINDB-15, 40, 50

Paraplegia:
NINDB-1, 2, 5, 21, 35, 54

Metabolic Diseases in General:
NIMH-15, 16, 17, 19, 23, 24, 25, 26, 27, 29, 30, 32
NINDB-11, 30, 31, 32, 33, 34, 36, 41, 44, 46

Diseases Other Than Neuropsychiatric:
NIMH-14, 17, 19, 34, 36, 39, 42, 76, 83
NINDB-9, 10, 30, 31, 32, 40

New Techniques:
NIMH-3, 4, 9, 21, 22, 93
NINDB-12, 13, 27, 33, 34, 38, 50

The work and progress in the individual disciplines are described in the reports of the laboratory chiefs which follow:

LABORATORY OF NEUROANATOMICAL SCIENCES

William F. Windle, Chief

The organization and staffing of the Laboratory of Neuroanatomical Sciences was nearly complete in 1955. Several junior positions remain to be filled and the Section of Neurocytology has not been fully activated. The chief of this section, Dr. Sanford Palay of Yale University, is temporarily serving as consultant and will come on full duty in the late spring of 1956. His move depends upon the completion of facilities for electron microscopy. As a part of this section, it is hoped that a tissue culture unit will be organized next year.

Functional Neuroanatomy. Without question the most significant contribution from the Laboratory of Neuroanatomical Sciences during the year 1955 is that by Dr. Grant L. Rasmussen. In his attempt to improve the Nauta stain for degenerating terminal fibers in the central nervous system, he discovered a way to stain all synaptic endings in section of formalin-fixed brain or spinal cord. He has been testing this method to determine its reliability and the results are satisfactory. For the first time it appears to be possible to see all the terminal endings of one neuron upon another. The method reveals a population of synaptic endings on large motor-type cells of the brain stem and spinal cord far greater than by any other technique. It has been consistently reproducible. This gives neurologists a new tool with which to investigate connections in the central nervous system. The tool may be applied to neuropathology to reveal subtle changes not ordinarily shown by the usual staining methods. This new method may hold as great promise for neuroanatomy as did discovery of the reduced silver staining methods in 1906 by Ramon y Cajal and Bielschowsky. It is noteworthy thatthis discovery was made by Dr. Rasmussen after he had come to this laboratory and it has been developed entirely in this laboratory. Additional personnel are being recruited to carry out investigations utilizing this new method.

Other accomplishments by Dr. Rasmussen are extension of his research on the recurrent or efferent nerve fibers which innervate the cochlea and the revelation of an orderly system of connecting neurons conducting impulses from the cerebral cortex to the cochlea. This system evidently represents an auditory feedback mechanism. In another project, Dr. Rasmussen is trying to demonstrate the pathway of autonomic innervation for the inner ear, especially the sympathetic component. It is strange that there is complete lack of anatomical information about this.

Experimental Neuropathology. Major efforts in the Section on Experimental Neuropathology were directed toward study of physical properties of the spinal cord in various species at different ages. These studies have included experiments on reactions to narcosis. Deep anesthesia resulted in volumetric changes in the spinal cord. These may well underlie other more subtle changes in the constituents of the spinal cord. The volumetric studies on the spinal cord provide basic information necessary for the understanding of responses of the organism to increase in age. The spinal cord rather than the brain was used because it is more adaptable to controlled experimentation.

Neurocytology. During 1955, Drs. Albers and Brightman developed a very sensitive bioassay technique for measuring antidiuretic hormones. It permits a number of determinations to be carried out on a single rat without any significant trauma and without anesthesia. With this new method, research has been directed toward determining whether circulating levels of posterior lobe hormones exert an effect on the output of these hormones and of neurosecretory material from the brain.

Dr. Brightman continued experiments which were reported last year and accumulated additional data on neurosecretory mechanisms. He developed a technique of irradiating minute areas in the rat's hypothalamus with x-rays, in an attempt to damage selectively the supraoptic and paraventricular nuclei of the hypothalamus.

Dr. Wayne Albers continued his work on development of new micro methods for determining pyridine nucleotide dependent enzymes in biological material, methods which are expected to extend studies of quantitative microbiochemistry of the nervous system. In addition, he carried out research on biochemical composition of histologically distinct elements of the nervous system and the manner in which these elements contribute to the biochemistry of neural function. It is expected that this project will contribute to our basic knowledge of the histochemistry of the nervous system.

Development and Regeneration. The law of "specific nerve energies" is a fundamental concept; it is thought that each end organ, after degeneration, regenerates only if located by its own specific type of nerve fiber. This is not necessarily true. Dr. Lloyd Guth demonstrated functional return in mammals after heterogeneous nerve anastomosis. No other adequately controlled experiment of this type has been reported. He showed that auricular vasomotor reflexes and pupillary reflexes of the cat, after inactivation by section of the cervical sympathetic trunk, were reactivated by fibers from the vagus nerve regenerating into the superior cervical sympathetic ganglion.

Studies on regeneration in the central nervous system were continued by Dr. Windle. The present status of central nervous system regeneration may be stated as follows: It has been proved to occur and involves essentially three mechanisms. In the very young individual soon after birth neuroblasts may still produce new nerve fibers, as has been shown in the first three weeks of life in the rat. Severed axons of nerve fibers in the central nervous system can send out new growths. Intact central axons adjacent to those which have been damaged are capable of sprouting new processes. The effective use of this regenerative activity is prevented in the higher animals, including the cat, monkey and man, by formation of neuroglial scars and later by encroachment of collagenous tissue. Since regeneration has been shown to be possible, it is now only a matter of time before ways are discovered to make it practicable. Research in this laboratory is being directed toward that end.

As part of the Neurological Institute's program of research in cerebral palsy and mental retardation, the Section on Development and Regeneration has undertaken to carry out certain basic studies. Drs. Windle, C. J. Bailey, and M. H. Hack have in progress experiments involving asphyxiation and resuscitation of fetal guinea pigs near the end of gestation. The animals are being reared for behavioral studies to determine possible alterations in learning ability and memory. The present study is an extension of Dr. Windle's earlier experiments of a similar nature.

During experiments to determine effects of bacterial pyrogens when administered to African green monkeys, occasion was found to utilize reserpine. The animals' reactions were such that a more extensive investigation of the effects of this and other drugs was undertaken. Doses of reserpine comparable to the same employed in human subjects produced in monkeys many of the symptoms of human parkinsonism. An effort is being made to determine whether or not cytological changes occur in the brain after chronic administration of the drug.

LABORATORY OF BIOPHYSICS

Kenneth S. Cole, Chief

The groundwork of the laboratory has been laid in its first year. The principal extensions of the staff nucleus are in progress, a large part of the basic equipment is available, and developmental, preliminary or experimental work is under way on the major phases of the laboratory program.

The squid giant axon is still the only preparation in which the ion movements fundamental to impulse excitation and propagation can be measured and analyzed. The primary effort of the laboratory is being devoted to means for obtaining the minimum necessary data on this axon with accuracy, rapidity, and reproducibility. The use of a micropipette as the control electrode has been found quite helpful for accuracy and speed, but places stringent requirements on the control circuits. Preliminary analysis of last season's data shows unsatisfactory survival and the needs for the development work now under way.

The calculation of nerve phenomena by the Standards Eastern Automatic Computer has shown the Hodgkin-Huxley equations to give a stimulus difference between passive and active responses that is many thousand times less than can be determined for the real nerves which gave rise to the equations. This indicates that some of the less factually grounded formulations of excitation may be inadequate. The theory and the calculations of the uniformly propagated impulse have been difficult and have progressed slowly.

The effects of a series of synthetic anti-cholinesterases on frog nerve impulse potential and velocity bear so little relation to the in vitro inhibition of the esterase by the compounds as to lessen the probability that acetylcholine is primarily involved in the activity phases of nerve impulse initiation and propagation.

Investigation of a 100 μ single nerve fiber from the lobster has been undertaken recently and the preparation shows considerable promise for the more precise investigation of the anticholinesterases and perhaps for the measurements of the ion movements underlying excitation.

LABORATORY OF NEUROPHYSIOLOGY

Wade H. Marshall, Chief

This laboratory, one of the first to be initiated in the program, saw an active and productive year. The areas of interest of its individual scientists cover the broad field of neurophysiology and interdigitate well with the Laboratories of Biophysics, Anatomical Sciences, Psychology, and Clinical Science. The interest in function of the nervous system ranges from studies on the mechanism of production of the action potential, the properties of single neurons, mechanisms of interaction between populations of neurons, action between neurons, the physiology of the visual system, the mechanism of action of hallucinogenic and other drugs, to the chemical and electrical properties of the cerebral cortex and the neurophysiological correlations or bases of behavior.

General Neurophysiology. The work of this section has been heavily involved in following up its previous contributions to the mechanism of hallucinogenic drug action. The resemblance between physiologically induced subnormality and that due to lysergic acid diethylamide showed the need for better information on the excitability cycles of the visual system. As a result of this work, a number of new and surprising facts have been revealed concerning the functional activity of the lateral geniculate body, the important relay station in the visual system. A prolonged and profound period of subnormality in this nucleus was discovered following tetanic stimulation for several seconds and has been studied intensively by Drs. Evarts and Marshall. The mechanism of this action is an extremely intriguing question which is being actively pursued. The answer will undoubtedly be very important for the understanding of the fundamental physiology of the synapse. Dr. Hughes and Dr. Evarts have made considerable advances in the knowledge of the phenomenon of post-tetanic potentiation, another phase of electrical activity at the synapse and critical to an appreciation of the relationship between synaptic transmission and psychological events.

During the past summer, Drs. Evarts and Shulman made a number of crucial observations on excitability cycles and LSD action in unanesthetized cats in which electrodes were implanted for stimulation and recording in the primary ascending visual system. This type of preparation is very important in order to eliminate anesthetic effects and to permit concurrent observations on behavior which are impossible in anesthetized preparations. The observations were very similar to those secured from brain stem section preparations. This information is not only of crucial value on those points but also relegates to a minor position the brain stem reticular mechanisms in these effects. This is important since some investigators have claimed that, if the brain stem reticular region were destroyed, lysergic acid would have no effect on the cat's brain. Thus, one of the achievements of this section has been to relieve the overloaded reticular system of two duties, control of the excitability cycle of the lateral geniculate and its reaction to lysergic acid. Dr. Leao, the discoverer of spreading cortical depression, is now working in this laboratory in collaboration with Dr. Marshall. This fortunate collaboration is making possible intensive work on oxygen tension changes as a function of neuronal activity and chemical alterations in them.

The Production of the Nerve Impulse. Dr. Tasaki is proceeding with brilliant experimental work designed to elucidate the mechanisms of production of the action potential in vertebrate nerve and muscle fiber. He believes that the evidence is now strong enough to indicate that the ionic theory is incapable of explaining his data on certain of these structures. Dr. Spyropoulos with the guidance of Dr. Tasaki has done a provocative piece of work on the effects of repetitive stimulation of isolated nerve fibers. These observations originated in the almost accidental discovery that prolonged stimulation produced a dramatic lengthening of the duration of the nerve impulse. He is now examining the effect of pressure on these action potentials, finding that high pressure shortens the prolonged spike while lengthening the normal spike.

Spinal Cord. This section under Dr. Karl Frank is one of the few to study electrical potentials of cell bodies and their fibers within the spinal cord and has developed techniques for making this type of measurement consistently. More important, they have developed adequate physiological tests and criteria for distinguishing between the reactions of cells and their fibers. Because of the relatively large size of motor neurons, most previous work on intracellular measurement has been concentrated on those cells. Dr. Frank's newer techniques have made it possible for this section to make systematic studies of the smaller interneurons. These important cells which stand between the sensory and the motor systems have been subjected to extensive study and classification. Many new properties have been elicited. A new type of cell which has been labelled an "alerting cell" has been described which responds to a wide field of peripheral stimulation and probably plays an important coordinating role in the nervous system. This section, in collaboration with Dr. Fuortes of the Walter Reed Medical Center, is pioneering in a study of the various types of rhythms initiated by the motor neurons. Studies of the trans-synaptic events in the spinal cord have yielded new information relating to the old question of how the nerve impulse is transmitted from one cell to another.

Cortical Integration. Dr. John Lilly and his staff have continued their work with the special electrical waveform for brain stimulation developed by them last year. It has been confirmed by them and others that this particular waveform is non-injurious. Other laboratories throughout the country have found this technique of value in permitting the stimulation of parts of the brain for research or diagnostic purposes without any evidence of injury.

In continuation of the cortical mapping studies on unanesthetized monkeys, this section has succeeded in implanting 610 electrodes over one hemisphere and has found that all areas of cortex give movements in response to electrical stimuli. The movements are appropriate for the area stimulated; i.e., eyes or ears move when the visual or acoustic receiving areas are stimulated. The frontal pole gave combined eye and ear movements. Post-central tactile cortex gave body movements similar to those of the classical precentral motor area. Studies thus far have indicated that a drastic revision of the classical motor areas of the brain will be necessary as the result of these unique studies now performed without the complications of anesthesia and acute surgery.

LABORATORY OF NEUROCHEMISTRY

Seymour S. Kety, Acting Chief

This laboratory deals broadly with the chemical structure and metabolism of the nervous system and the biochemical processes which are involved in normal and abnormal mental and neurological function. Its program extends from extremely basic physical chemistry of various components important to the nervous system and to the body as a whole, through biochemical processes which occur in isolated chemical systems or cells to the intact human brain.

Physical Chemistry. This section has continued its general program on the structure of molecules of biological importance with emphasis upon those materials which are vital to an understanding of the structure and function of nervous tissue. The main concern of the group under Dr. Rich has evolved about ribonucleic acid, a large molecule which is found inside all cells and which appears to be associated with protein synthesis. This material makes up the Nissl substance which is so pronounced a feature in certain types of nervous cells. X-ray diffraction studies of synthetic materials which have been formed by an enzyme and are composed of the same units as natural nucleic acid have been carried out. These materials were found to have the same structure as the substance isolated from natural sources. This finding is significant in that it suggests that the native substance does not have the structure based upon a specific union between various parts of different molecules.

Two significant structural discoveries were made which are important in the field of connective tissue. The structure of a synthetic polypeptide, polyglycine II, was determined. This material has in it long, helical molecules which are held together side to side in a specific manner utilizing hydrogen bonds. As a result of this discovery, a structural model has been proposed for collagen, the major fibrous protein molecule of skin, connective tissue, tendons, blood vessel coating, etc. Collagen has 33% glycine, and the proposed model consists of three polypeptide chains approximately arranged as in the polyglycine crystal. This model predicts the correct X-ray diffraction pattern, infrared spectrum and amino acid sequences which are found in collagen itself. In view of this, it is highly likely that it is the correct structure, and it will serve as a great stimulus to research in this field.

Another project in this laboratory has been the study of the diffusion properties of lipid containing membranes. Nerve cells have at their surface a membrane which is coated with lipid and which conducts ions during the transmission of the nerve impulse. Model diffusion systems have been set up in an attempt to learn how these membranes act when transferring ions.

Lipid Chemistry. This section under Dr. Roscoe Brady is primarily interested in the metabolism of complex cerebral lipids, and its first concern at this time is a knowledge of the intermediary pathways by which lipid synthesis takes place and the forces which regulate and supply the energy necessary for those processes. This section has undertaken and completed some fundamental studies on the metabolism of substituted derivatives of acetyl coenzyme A, the high energy building block of long chain fatty acids. These studies have yielded insight into the nature of some enzyme-substrate kinetics of coenzyme A complexes. Furthermore, in the course of these studies, two new naturally-occurring enzymes have been discovered; one catalyzes the biosynthesis of abnormal coenzyme A compounds such as fluoroacetyl coenzyme A and another oxidizes specifically the 2-mercaptoethylamine moiety of coenzyme A. The latter is of particular interest because coenzyme A must be in the reduced state for the formation of high energy thiol esters which have proven to be so essential for many biological energy yielding processes such as the oxidation of carbohydrate and fatty acids as well as fatty acid synthesis and the formation of acetyl choline.

Further work has been performed on the cofactor requirements for fatty acid synthesis, and several profound effects have been observed upon the addition of supplemental coenzyme A or reduced triphosphopyridine nucleotide on the process. With a knowledge of these facts, a reasonable explanation of the failure of fatty acid synthesis in diabetes may be obtained.

Extending the basic knowledge of fatty acid synthesis to the formation of the cerebral lipids, two new complicating materials are introduced. This section would like to learn how cerebrosides are synthesized and subsequently metabolized by the brain. To study this process, Dr. Brady's group has prepared and performed enzyme studies with uridine diphosphogalactose labelled with radioactive carbon-14. The formation of this substance has been investigated in extracts of brain tissue, and the results of the study have been published. Further work on the incorporation of galactose into cerebrosides is in progress.

The third component of cerebrosides in addition to a molecule of fatty acid and galactose is sphingosine. A method has been developed in this laboratory for the purification and microanalysis of sphingosine. The material has been used for the model synthesis of C^{14}-labelled ceramides which are amide complexes of a fatty acid with sphingosine; in other words, a cerebroside minus the molecule of sugar.

The study of cerebrosides is to be approached from all three angles; i.e., fatty acid metabolism, sphingosine metabolism and finally carbohydrate metabolism. This section has discovered a new enzyme in mammalian tissue which catalyzes the phosphorylation of ribose. The enzyme has been purified, characterized, and the product ribose-5-phosphate conclusively identified. This enzyme is extremely important because ribose forms an integral part of nucleic acids and the nucleotide coenzymes. Among the latter are adenosine triphosphate, diphospho and triphosphopyridine nucleotides whose paramount importance in energy transfer and biological oxidations is indisputable. This study is being extended to obtain knowledge of the formation and concentration of these and other nucleotides in the brain during development and under normal and pathological conditions. The importance of these compounds in the regulation of nerve metabolism merits careful investigation at this time.

Cerebral Metabolism. The activities of this section are concerned with the metabolism of the living brain in situ. Its program includes continued observation on the human brain by the use of the nitrous oxide technique and a continuing effort to study the circulation and metabolism of the separate areas of the brain in the living and functioning state. Studies of the effects of lysergic acid diethylamide in normal and schizophrenic subjects have been completed. During the peak of the psychological effects of this substance, no detectable changes in circulation or metabolism were revealed. This finding is of some interest since there has been much speculation on the mechanism of action of this substance and studies on isolated tissue have suggested the possibility that it may act either by affecting the circulatory state of cerebral vessels or by interfering with oxidative metabolism. Further data was obtained on the interesting association between marked anxiety and cerebral oxygen consumption.

Additional work has been done on the technique for rapid continuous measurement of cerebral blood flow in man developed by Doctors Sokoloff and Kety in collaboration with Dr. Benjamin Lewis of the U.S. Naval Air Development Center. During the past year the method, which involves the use of a radioactive gas (Kr^{79}), has been found capable of demonstrating the rapid changes produced in cerebral blood flow by hyperventilation and by drugs such as carbon dioxide and nor-epinephrine and to follow these changes over minute-to-minute intervals. This technique which is of great value in aviation physiology will also find application in numerous types of neuropsychiatric conditions in which rapid alterations in the cerebral circulation may be examined.

Doctors Kety, Sokoloff, and Freygang have continued their studies on the local circulation of the brain. Experiments in large numbers of cats, both conscious and anesthetized, have demonstrated that the method yields reasonable and consistent values. Blood flow in approximately 28 individual structures of the brain and spinal cord has been measured for the first time and changes in local blood flow attending alterations in physiological and pharmacological states have been demonstrated. Values obtained in the areas of the cerebral cortex generally associated with sensory-motor, visual or auditory functions were very high, surpassed only by those of the inferior colliculi and greatly exceeding values in other areas of the cortex. Retinal stimulation in similarly anesthetized cats by means of strong repetitive light flashes appears to result in increased visual cortical blood flow particularly in tiny, discrete, punctate areas in the lateral gyri. This strongly suggests a relationship between local cerebral blood flow and functional activity.

Dr. Sokoloff has continued his studies on the possible mechanism of action of thyroxine and its relationship to cerebral metabolism. He has demonstrated for the first time, by measurement of the uptake of radioactive thyroxine, that this substance does penetrate the blood:brain barrier. The results further suggest that the turnover rate of thyroxine in brain is similar to those in liver and kidney, tissue whose metabolism is markedly affected by thyroxine. Thus, his finding, several years ago, that thyroxine does not increase the metabolism of the brain in contradistinction to its effects on other tissues must be explained upon some inherent property of cerebral metabolism rather than an inability of this hormone to cross the blood:brain barrier.

LABORATORY OF CELLULAR PHARMACOLOGY

Giulio L. Cantoni, Chief

This report covers the first full year of operation of the Laboratory of Cellular Pharmacology. It is gratifying to report that the initial phase of the work has been completed, that numerous projects have been initiated, and that satisfactory progress has already been achieved in some of them. Research activities of the Laboratory of Cellular Pharmacology have been developed in three main areas: 1) studies on biological methylations, 2) studies in comparative biochemistry, and 3) studies of the interrelationship between amino acid metabolism and the citric acid cycle. These three areas have been chosen because of their particular interest to problems of cellular and neuropharmacology and also because they are contiguous rather than separate areas of biochemical research.

Biological Methylation Mechanisms. There is every reason to believe that the biosynthesis of neurohormones such as acetylcholine and epinephrine, the biosynthesis of alkaloids such as morphine, nicotine, bufotenine and many others, and the formation of thiamine may involve transmethylation reactions. Furthermore, it has been suggested that the cleavage of "onium" compounds may be responsible for some of the physicochemical changes which accompany such processes as nerve conduction and muscle contraction. While this suggestion is no more than a working hypothesis, it is obviously of great interest to cellular physiology in general and to neurophysiology in particular.

Recent work on the pharmacology of hallucinogenic agents raises the possibility that a closer and exciting relationship between biological transmethylation and mental health may develop. This possibility at present rests purely on hypothetical grounds and may be formulated as follows: Most of the naturally occurring hallucinogenic agents are known to contain either one or several methyl groups attached to a nitrogen and/or to an oxygen atom. It is safe to assume that biologically these methyl groups are derived from methionine. One can therefore propose as a working hypothesis the idea that in some types of mental disorders the underlying biological derangement is a defect in the metabolism of the "labile" methyl group. This hypothesis may be accessible to an experimental approach because it may be possible to interfere with metabolism of the methylated compound by administration of large excess of compounds which are capable of acting as methyl acceptors. In man, one might use compounds such as nicotinamide or guanidino acetic acid which are excreted as the N-methyl derivatives, (N-methylnicotinamide and creatine respectively). In fact, it has been reported that administration of large doses of nicotinamide results in considerable improvement in certain types of schizophrenia. It is not clear, however, whether this improvement is related to the methylation of nicotinamide or to some other cause. Plans are being made to attack the problem in collaboration with the Laboratory of Clinical Science.

Comparative Biochemistry. It is not necessary to emphasize the relationship between comparative biochemistry and cellular pharmacology. Indeed, it can be stated that rational use of drugs depends upon the understanding of the metabolic differences between different tissues and different species.

Experimentally, an approach to comparative biochemistry is underway and it is hoped to develop this area of research further in the coming year. The project on atropine esterase in the rabbit and its genetic determination appears of particular interest in this connection.

Amino Acid Metabolism and the Citric Acid Cycle. The third broad area of interest has been the field of amino acid metabolism in general and, in particular, the relationship between individual amino acids and metabolites of the citric acid cycle. Studies of this kind are also related to comparative biochemistry because one of the characteristic features of mammalian metabolism is the relative inability to synthesize amino acids whereas in lower species this ability is widespread. Of particular significance to mental health are the studies on the metabolism of phenylalanine for it is generally agreed that a defect in the metabolism of this amino acid is involved in one form of mental deficiency in children. Dr. Kaufman has already achieved considerable progress in this area.

During the next twelve months, it is hoped to initiate new projects to include the biology of thyroxin, the biosynthesis of alkaloids and animal hormones, and the formation of adaptive enzymes in the mammal.

ADDICTION RESEARCH CENTER

Harris Isbell, Chief

Addiction Liability Testing. The original object of this program at the Addiction Research Center was to develop a pain-relieving drug which would not have the addictive properties of morphine. There now seems little hope that such an agent can be found because six different chemical classes of analgesics have been shown to possess addiction liability. The program is now being carried on for the protection of the public with the object of preventing introduction of potentially addicting substances into uncontrolled clinical use. Drugs are referred to the Center by the Committee on Drug Addiction and Narcotics of the National Research Council. After the addictive potentialities of new drugs have been investigated, reports are sent to that committee who in turn forwards them to the Section on Addiction-Producing Drugs of the World Health Organization. The Committee on Drug Addiction and Narcotics and the Addiction-Producing Drug Section, WHO, then advise the U.S. Government and the United Nations respectively concerning appropriate legal action at the national and international levels.

During the year eleven new drugs were tested. Seven of these had addiction liability in some degree. Two of these are of particular chemical and pharmacological interest, since in both drugs substitution of a phenethyl group for the methyl on nitrogen enhanced both analgesic activity and addictive potentiality. Both drugs can be produced more cheaply than codeine. Both have been shown to have analgesic properties in clinical practice. They are very promising substitutes for codeine and, therefore, important to the project which is being carried on for the Office of Naval Research.

Four drugs had no addiction liability. One of these was papaverine, the other three were members of the hexamethyleneimine series. The hexamethyleneimines are being watched with interest since they are reported to be effective clinical analgesics. Studies on the analgesic properties of these drugs, however, have been very poorly conducted and poorly controlled. It seems likely that they actually will not be useful pain-relieving drugs.

Neither chlorpromazine nor reserpine were found of value in the treatment of acute abstinence from morphine. In fact, reserpine made withdrawal symptoms worse, probably because side effects of reserpine synergize with the withdrawal symptoms.

Chronic Barbiturate and Alcoholic Intoxications. In previous years this laboratory has shown that severe symptoms follow withdrawal of barbiturates from chronically intoxicated persons who have ingested 0.8 gram or more of the potent barbiturates daily for two months or more. Occasionally severe symptoms followed withdrawal of barbiturates from persons who were taking 0.6 gram daily. During the current year it was found that symptoms following withdrawal of barbiturates from persons taking 0.4 gram daily are quite mild. Barbiturate addiction may now be defined quantitatively. Persons ingesting 0.8 gram of a barbiturate or more daily should be regarded as being strongly addicted; those taking 0.6 gram daily as mildly addicted; and those taking 0.4 gram or less daily should not be regarded as being addicted.

Four dogs were chronically intoxicated with alcohol for 65 days. On reducing the dose of alcohol all four dogs showed tremor, weakness and peculiar behavior. Following abrupt withdrawal of alcohol after increasing the dose, anorexia, tremor, nervousness, fever, and insomnia were observed in all four dogs. One dog had sixteen convulsions and bizarre behavior characterized as "canine delirium" appeared in two. These experiments show that it is possible to develop physical dependence on alcohol in dogs.

Intoxicants Other Than Analgesics, Barbiturates, and Alcohol. Major interest in this field continued to be centered on the diethylamide of lysergic acid (LSD-25). Combinations of LSD-25 with a number of drugs were studied in the hope of either blocking or enhancing the LSD reaction. In either event, useful information concerning the mode for action of LSD might be obtained.

A strong trend toward reduction in the intensity of the LSD reaction was seen after administration of chlorpromazine both orally and intramuscularly. Reserpine in doses up to 6 mg. orally had no significant effect on the LSD reaction. When, however, 7.5 mgm. of reserpine was given intramuscularly, prior to administration of LSD, the LSD reaction was more severe.

Twenty mgm. of 4-Piperidyl-Diphenylcarbinol (Frenquel) three times daily for seven days prior to administration of LSD did not significantly affect the intensity of the reaction. A "double-blind" study is now being conducted in which 60 - 100 mgm. of this drug is being given at the height of the LSD reaction. No clearcut evidence of any spectacular diminution in LSD effect has yet been observed.

Biochemistry of Addiction. Work in this field is in transition from clinical chemistry of addiction to studies on degradation of various drugs on the body and to the cellular chemistry or enzymology of addiction. Further information on the clinical endocrinology of addiction was obtained. The results continue to indicate pituitary depression during maintained addiction which affects the adrenals and gonads more than it does the other endocrine glands. Following withdrawal of morphine, the pituitary seems to be released from the depression and marked activation of the adrenal occurs.

Neurophysiology and Neuropharmacology of Addictions. During the year studies on the neurophysiology of barbiturate addiction were begun. Cats chronically intoxicated with barbiturates for 2-5 months had convulsions following withdrawal. Development of this condition in cats is a great advantage since neurophysiological technics are more readily applied to cats than to dogs.

Psychiatry and Psychology of Addiction. During the initial days of chronic intoxication with 0.4 gram pentobarbital daily marked impairment of visual-manual reaction time and tests of motor coordination was observed. Tolerance to these effects developed quite rapidly and no significant impairment was observed following withdrawal of the barbiturates.

Studies described in the last annual report on Effects of Motivation on the Actions of Drugs were extended. It was found that either morphine or pentobarbital could act as a "stimulant" or "depressant" (in measurements of visual-hand reaction time), depending on whether subjects were motivated to cooperate in "low", "high", or ordinary degree.

Studies on the effects of drugs in restoring inhibition of conditioned feeding response in rats were greatly extended during the year. It was found that various classes of drugs induce specific patterns of effects.

LABORATORY OF CLINICAL SCIENCE

Edward V. Evarts, Acting Chief

This laboratory supported by the basic program as well as the program of clinical investigations of NIMH has as its broad responsibility the areas of interaction between the biological and the mental sciences. Many of its staff are trained in clinical psychiatry in addition to their training in one of the biological disciplines and the several disciplines of biochemistry, pharmacology, physiology, psychology, and psychiatry are well represented on the staff. With the multidisciplinary representation in a single laboratory, the fundamental contributions of basic research may be continuously related to clinical problems. A summary of the activities of two of the sections appears below. The other sections are included in the report of the Clinical Director, NIMH.

Clinical Biochemistry. Dr. Kies has continued the active interest of this section in the phenomenon of allergic encephalomyelitis, a demyelinating disease produced in animals by the injection of brain extracts and related quite obviously to the clinical diseases of multiple sclerosis, and the demyelinization in certain types of mental retardation, infectious processes and nutritional deficiencies of the brain. Considerable progress has been made by this section in characterizing the nature of the active substance in brain which produces this experimental disease. An incidental finding of great significance is the remarkable elevation of lipids to values 40 times the normal following the administration of this antigen. This finding, hitherto unreported, appears to be of major importance in the process of this demyelinating disease and has obvious implications to the little understood phenomenon of lipemia seen in a number of general metabolic diseases. In another project of this section, it is found that lysergic acid diethylamide had strong anti-diuretic effects in normal individuals. The possible relationships of this finding, which suggests an involvement of the hypothalamus and pituitary glands in LSD induced psychosis, are being actively pursued.

Clinical Pharmacology. This section under Dr. Axelrod has concerned itself with the metabolism, fate, and mechanisms of action of drugs which affect mental state, and the biochemical aspects of drug addiction. In the previous year, Dr. Axelrod has characterized a microsomal enzyme system which is involved in the transformation of many of the narcotic drugs and is now continuing other studies in this area. Ololuiqui, a narcotic seed used in ancient times by the Aztecs for mental effects, has been subjected to careful study. Preliminary experiments have shown that extracts of the seed produce a state of catatonia in some lower animals without diminution of consciousness. Steps are being taken toward the isolation of the active principle in the seed.

Studies on the disposition of lysergic acid diethylamide, using a specific spectrofluorometric method developed by this laboratory and capable of detecting infinitesimal quantities of the substance, have shown that LSD readily crosses the blood:brain barrier but is not selectively concentrated in the brain. In vitro studies have revealed that LSD can be transformed by a microsomal enzyme system present in the liver of a number of mammalian species. The isolation and characterization of the products of this substance are actively under way. Such studies devoted to the possible mechanisms whereby this substance produces effects similar to those seen in schizophrenia are important in the possibilities which they present of elucidating possible biochemical pathways for the manifestations of mental illness.

In a study on the biochemical factors involved in the development of tolerance and addiction to narcotic drugs, the enzyme system for the demethylation of morphine, previously described by Dr. Axelrod, has been studied under various conditions. Animals made tolerant to morphine were found to have markedly reduced activity of these demethylating enzymes. These studies have only recently been undertaken. They offer a unique and promising approach to the problem of narcotic addiction.

LABORATORY OF PSYCHOLOGY

David Shakow, Chief

Since the last annual report the laboratory has continued through further stages of organization and stabilization. As was indicated last year the breadth of activity of the laboratory is great; it ranges within the field of behavior from the molecular through the molar to the social, it involves the normal as well as the pathological, it requires going into the field as well as carrying on studies in the laboratory and on the wards. Further, because of the stage of development of the field as a whole, it must concern itself heavily with methodological as well as with substantive problems. Some of the studies are being pursued independently or jointly within the laboratory itself; many involve collaboration with other laboratories or even other Institutes.

Aging. This section now contains a group of investigators whose specialization in fundamental studies of aging of the nervous system has helped make expert opinion available to other institutions and investigators in an area now assuming increasing public significance.

For mammals, man in particular, the nervous system is a natural focal point for behavioral and biological studies of aging. The nervous system is of dual interest because of the likelihood that it contains the general pacemaker of aging as a result of its role as an integrator of somatic function, and also because of the prime importance of age changes in mental processes. The Section on Aging is attempting to gain an understanding of the factors affecting aging of the nervous system.

Since the nervous system acquires or learns many of its functions, it is necessary that both social input as well as the biochemical processes be explored in identifying the major variables governing aging of the nervous system. Studies of the section require observations of different species of animals, normal and pathological stages, and animals in which changes to simulate aspects of aging are experimentally induced.

The actual projects now in progress include studies of both a psychological and of an organic nature. On the psychological side, age changes in mental and perceptual abilities and personality structure serve as a basis for correlation with physiological variables and psychiatric states which are being carried out by other laboratories. A special study is being made of age changes in time-intensity relations in human perception based on the hypothesis of the importance of slowing in stimulus perception and response time. Age changes as affecting the behavior of the rat in such areas as spontaneous activity, speed of response, learning and memory, are being carried out concurrently with the human studies.

On the organic side, investigations are in progress on cytological and cytochemical changes in the nervous system as a function of age, on the metabolism of neuropharmacological agents as a function of age, on metabolism of nervous tissue as a function of age, and on age changes in brain electrolytes of rats.

Mature Organism. Although a considerable number of studies are being carried out at the two ends of the biological cycle, the development and the aged, by the sections primarily devoted to these areas, the major activity of the laboratory is directed to studies of psychological function in the mature organism, both normal and pathological. These involve human and animal subjects, both under individual and social conditions.

In the studies of individual human subjects a systematic experimental study is planned on the processes by which a person comes to differentiate among the various stimuli in his environment. These differentiations are to be related to his history of exposure to the stimuli, to stimulus complexity and to verbal identifiability of the stimulus patterns. Another study is directed at quite another aspect of the problem of perception: the testing of Kohler's satiation theory. Data from such a study could contribute to the development of a sound theory of normal processes of perception.

With animal subjects studies are being carried out on discrimination processes and on the utilization of space. The former study, in pigeons, is particularly concerned with the identification of basic mechanisms in discrimination learning. The latter study, being carried out with rats, is directed at determining the duration and frequency of behavior of rats in relation to their distribution through space in an unstructured environment. With these measures as a base line, it will be possible to measure the effects of various stimulus-response situations, motivation, drugs, etc. Thus far, in the latter experiment, it has been found that the frequency of trips is inversely proportional to the distance of termination. These base lines are affected by changes in the intensity of light, age differences, and genetic strain differences.

Several studies are in progress which relate to social organization in animals. One is concerned with the population dynamics of vertebrates living under natural conditions and is based on the coordination of data from a large number of field activities scattered over North America. Another, an experimental investigation, deals with the physiological and behavioral consequences of group formation in mice. The objective is to determine the consequences of varying the number of mice from 1 to 32 in a standard-sized field.

Some aspects of the previous projects had the additional goal of achieving methodological refinement. A special project has been organized to develop an adequate means of recording eye movements and eye position electrically because of the possible importance of such a technique for studying the perceptual process independently of conscious report.

Pathological. Our studies on pathological material embrace, on the one hand, both psychological functioning as found in natural pathological conditions such as are represented in various forms of mental and physical disorder, and functioning in instances where the pathology has been experimentally produced. On the other hand, the studies also involve aspects of attempts to modify such pathology by either psychological or other means.

In the program of study being carried out by the Section on Animal Behavior, extensive work is being done on brain-damaged human subjects who are being studied by means of a continuous visual discrimination task. Although a more flexible and comprehensive apparatus is being developed the present instrument is being used with a variety of patients undergoing temporal lobe surgery. The instrument seems to offer promise of providing a fairly simple and reliable device for assessing effects of brain damage in human subjects.

The work of the Section on Animal Behavior consists mainly of studies of psychological function as related to brain structure -- particularly of ablated structure. Studies are in progress on the identification of the brain structures of sub-human primates which subserve emotional behavior, intelligent behavior, social behavior, visual and auditory functions. Associated detailed histological analysis is being carried out. A set of studies is also being completed which is concerned with detailing the functions of the cortical "association" areas in monkey and man.

Two studies involving drug interventions are in progress. The first of these is part of a study of the effects of lysergic acid on visual function. The attempt was made to make more specific the subjective distortions frequently reported with the administration of LSD. Such visual functions as dark adaptation, visual acuity, depth perception and size-constancy under LSD were studied precisely and quantitatively. The findings indicate that LSD produces a stable difference in absolute visual threshold throughout the course of dark adaptation. The other study using drugs is on the visual discrimination processes of pigeons under the effects of nembutal and alcohol. Both of these decrease the pigeons' accuracy on a complex visual discrimination, while at the same time increasing the total output of responses.

LABORATORY OF SOCIO-ENVIRONMENTAL STUDIES

John A. Clausen, Chief

The core program of the Laboratory of Socio-environmental Studies is based upon three general propositions as to the relationship between mental health or illness and the social order: 1. The conditions of life and the patterning of relationships in the family and in the larger society affect (a) the vulnerability of the individual to certain forms of mental illness (or other maladaptive responses), (b) the precipitation of mental illness and (c) the duration of such illness; 2. The social organization of treatment services for the mentally ill (hospitals, clinics, etc.) and the patterning of beliefs, attitudes and behaviors of personnel who interact with mental patients influence the desire and ability of those patients to relate to others and to cope with their illness; 3. Mental illness is manifest in the disordering of the person's ability to carry out his normal social relationships and the responsibilities they entail. The nature of prevailing beliefs about mental illness, and the nature of the society's efforts to deal with such illness influence both the initial disruptiveness of the illness and the rehabilitation of the patient.

These propositions are not in any way intended to minimize the role which organic processes may play in etiology or in treatment. In some instances of mental illness, organic or constitutional factors may be of pre-eminent importance; in other instances there would seem to be an interaction of social, psychological and organic processes through the mediation of personality functions.

Social Development and Family Studies. In general this section engages in intensive research on human behavior in small, relatively close-knit groups, focusing especially on changes in psychological status which accompany developmental stages, transitions or stressful situations. It studies how changing capacities, expectations, responsibilities and relationships influence the psychological demands placed upon the person and the consequences for his mental health.

During 1955 substantial progress was made in the analysis and reporting of the long-term study of the impact of mental illness upon the family, a study directed jointly by Doctors Clausen and Yarrow. Several new studies were initiated during 1955. One, developed by Dr. Jordan in collaboration with the Children's Service, Clinical Investigations Branch, has adapted field observational and recording techniques to the study of adult attempts to influence the behavior of the acting-out aggressive children on the ward. In another collaborative project, Dr. Quinn has collected observational and interview data on the social relationships during treatment of identical quadruplets under the care of the Clinical Investigations Branch. In the planning stage is a study of the functioning and adjustment of older persons living in the community.

Community and Population Studies. In general, this section studies the effect of broad aspects of social organization and the cultural order upon mental health or illness. This entails the delineation and analysis of psychologically significant aspects of life in distinct populations, strata or groups characterized by socio-economic status, ethnic origin or community of residence or subject to common stresses. In addition to basic research which bears upon questions of etiology, the program of the section includes research on the utilization of effectiveness of health services in the community.

During 1955, Doctors Clausen and Kohn carried out further analysis of data relating to the social backgrounds of schizophrenic patients hospitalized from Hagerstown, Maryland. Dr. Youmans substantially completed his study of the administrative careers of persons trained in the management intern program sponsored by the Civil Service Commission. Dr. Linn worked with personnel of the Office of Health Emergency Planning and the National Research Council Committee on Disaster Studies to investigate community response to health emergencies in two areas: (1) following the disastrous floods in Connecticut in late August and (2) following the postponement of the opening of public schools as a result of concern over polio incidence in the Boston area in September.

Social Studies of Treatment Settings. In general, this section is concerned with the institutional process of dealing with mental illness. Research interests include studies of the influence of social factors on the forms and effectiveness of treatment provided the mental patient, studies of the patient's adaptation to the hospital world and its consequences for rehabilitation, and studies of organizational forms and staffing arrangements that make for effective achievement of therapeutic objectives.

Dr. Goffman described some of the norms regulating interaction among patients and staff, focusing upon the types of corrective mechanisms that occur when infractions of the rules arise. Mrs. Schwartz described and analyzed the responses of nursing personnel to an attempt to alter the traditional nursing role on a small ward for schizophrenic patients. Dr. Deasy completed interviewing and coding of data on her study of the relationship between nurses' and aides' perceptions of given psychiatric patients and their functioning with these patients.

Genetics of Mental Deficiency. Dr. Gordon Allen completed clinical investigations and continued analysis of data in his twin study of mental deficiency at the New York State Psychiatric Institute. Principal findings during the year have related to mongolism and are based on 39 mongoloid index cases and their siblings, representing 32 multiple births.

SECTION ON TECHNICAL DEVELOPMENT

Michael M. Davis, Jr., Chief

This section, whose purpose is the development in collaboration with the various laboratories of new techniques for the solution of scientific problems, has had a productive year, undertaking some 90 projects of an original, developmental nature. The section has fulfilled its other obligations of the maintenance, repair, and modification of the program's large investment in research instruments. Availability of the engineers and technicians in this section for consultation has been of great value to the other scientists.

As examples of the type of instruments developed by this section, for which no counterpart exists, is an analogue computer which solves the complicated mathematical equations involved in the measurement of local blood flow in the brain. Although designed for highly specialized use, this computer is versatile in that it may form the basis for numerous other computations by the addition of other computer elements suitable for the particular problem. Another instrument was an automatic paper strip analyzer for paper strip electrophoresis techniques using radioactive tracers. This instrument makes possible day and night runs with the equipment unattended with a great saving in time and efficiency. This section has developed an automatic starter for high speed centrifuges which does away with the manual and unprecise control of initial power to the centrifuge in order to attain a high enough speed without overloading the motor. In conjunction with the Laboratory of Biophysics, this section has developed a number of techniques for the efficient recording and analysis of many kinds and numbers of data. In the development by the Laboratory of Neuroanatomical Sciences of a method for the assay of minute quantities of anti-diuretic substance in blood, a method was required which would accurately maintain the animal's water balance. An apparatus was designed which counts the drops of urine excreted and injects back into the animal an amount of fluid appropriate to maintain its fluid balance. The apparatus is entirely automatic, repeating the cycle as urine is excreted. Since so much of modern research depends upon the development of highly specialized and precise methods, the work of this laboratory and its value to the program as a whole cannot be overestimated.

Research Project Reports - 1955

NIMH-NINDB Basic Research Program

Project No.	Project Title
NIMH-1	Excitability and interaction of neurons of the central nervous system using chronically implanted electrodes in cats.
NIMH-2	Recovery cycle of lateral geniculate nucleus of the cat and bilateral interaction in same.
NIMH-3	Cortical physiology.
NIMH-4	Intracellular recording from cortical neurons.
NIMH-5	Simultaneous recording of action potential and membrane impedance in the squid giant axon; effects of current flow.
NIMH-6	Effect of temperature on membrane and protoplasmic resistance.
NIMH-7	Effects of drugs on ion specific conductances.
NIMH-8	Resistivity of cerebral cortex.
NIMH-9	Relations between electrical stimuli, behavior, and the electrical activity of the brain of unanesthetized monkeys.
NIMH-10	(Proposed) Investigation of the influences of midbrain and fornix systems on emotional behavior in the unanesthetized monkey.
NIMH-11	Establishment of a near zero level of physical stimulation and its effects on brain activity.
NIMH-12	Determination of the structure of ribonucleic acid.
NIMH-13	Determination of the molecular structure of polyglycine II.
NIMH-14	Determination of the structure of collagen.
NIMH-15	Determination of the structure of coordination compounds of metals and of other biologically important substances.
NIMH-16	The metal complexes of nucleosides, nucleotides, and nucleic acids.
NIMH-17	Changes in nucleic acid structure.

Project No.	Project Title
NIMH-18	Diffusion properties of lipid membranes,
NIMH-19	Fractionation of ribonucleic acid.
NIMH-20	Studies on the circulation and metabolism of the human brain: I. Effects of lysergic acid diethylamide and other hallucinogenic drugs on cerebral circulation and metabolism and psychological phenomena. II. Effects of anxiety on the cerebral circulation and metabolism. III. Age changes in cerebral blood flow and metabolism.
NIMH-21	Measurement of local circulation in the brain.
NIMH-22	The rapid continuous measurement of cerebral blood flow in man.
NIMH-23	The mechanism of action of thyroxine and its relation to cerebral metabolism.
NIMH-24	Studies on the mechanism of the methionine activating enzyme.
NIMH-25	The mechanism of succinyl coA deacylase
NIMH-26	Study of methionine synthesis by enzymatic transmethylation from betaine or dimethylthetin.
NIMH-27	The metabolism of S-adenosylhomocysteine, a product of transmethylation reactions involving "active methionine".
NIMH-28	Organization of the laboratory "tooling up" and preparation of enzymes.
NIMH-29	The conversion of glycine to acetate.
NIMH-30	The conversion of phenylalanine to tyrosine.
NIMH-31	Chemical studies on patients with acute and chronic schizophrenia as well as chronic demyelinating diseases, e.g. multiple sclerosis, Guillian-Barre' syndrome and post-infectious encephalitis.
NIMH-32	Role of the adrenal medulla in reaction to stress.
NIMH-33	Fractionation of brain constituents. Isolation and identification of antigen responsible for production of allergic encephalomyelitis.

Project No.	Project Title
NIMH-34	Identification of abnormal lipid constituents in blood and brains of animals suffering from allergic encephalomyelitis.
NIMH-35	Immunological studies on allergic encephalitis.
NIMH-36	Antidiuretic effects of LSD in normal and schizophrenic subjects.
NIMH-37	Changes in blood protein of animals with allergic encephalomyelitis.
NIMH-38	Investigation of chemical changes in cerebrospinal fluid of animals suffering from experimental allergic encephalomyelitis.
NIMH-39	Cellular mechanisms in the metabolism of drugs.
NIMH-40	Studies on ololuiqui, a narcotic seed of the Aztecs.
NIMH-41	Studies on physiological disposition and metabolic fate of lysergic acid diethylamide.
NIMH-42	Studies on physiological disposition and metabolic fate of papavarine.
NIMH-43	Studies on the biochemical factors involved in the development of tolerance to narcotic drugs and the action of narcotic drug antagonists.
NIMH-44	Neurophysiology and neuropharmacology of addiction.
NIMH-45	Psychological studies of addiction.
NIMH-46	Studies of acute and chronic intoxication with drugs other than alcohol, barbiturates or analgesics.
NIMH-47	Addictive liability of new analgesics.
NIMH-48	Chronic intoxication with barbiturates and/or alcohol.
NIMH-49	Biochemistry of addiction.
NIMH-50	The analysis of the relationship between emotional behavior and certain cortical and subcortical structure in the subhuman primate brain.
NIMH-51	The analysis of the relationships between intelligent behavior as demonstrated in the delayed response and discrimination tasks and certain cortical and subcortical structures in the subhuman primate brain.

Project No.	Project Title
NIMH-52	The effects of immediate postoperative experience on dominance behavior in monkeys with anteromedial temporal lobe lesions.
NIMH-53	Further analysis of continuous performance test function in brain-damaged patients.
NIMH-54	Cerebral organization in audition.
NIMH-55	Contributions of an extrageniculo-striate system to vision.
NIMH-56	Completion of analysis of the behavioral effects of lesions in the association cortex of monkeys and man.
NIMH-57	Histological analysis of brain lesions in primates.
NIMH-58	Age changes in mental and perceptual abilities and personality structure.
NIMH-59	Age changes in time-intensity relations in human perception and responses.
NIMH-60	Cytological and cytochemical changes in the nervous system as a function of age: An investigation of submicroscopic morphology employing the light and electron microscopes.
NIMH-61	The metabolism of neuropharmacological agents as a function of age.
NIMH-62	Metabolism of nervous tissue as a function of age.
NIMH-63	Age changes in brain electrolytes in the rat.
NIMH-64	Age changes in the behavior of the rat: Spontaneous activity, speed of response, and learning and memory.
NIMH-65	Effects of lysergic acid diethylamide (LSD-25) on visual functions.
NIMH-66	Test of the satiation theory of perception.
NIMH-67	Electrical recording of eyemovements.
NIMH-68	Population dynamics of vertebrates living under natural conditions.

Project No.	Project Title
NIMH-69	Physiological and behavioral consequences of group formation (in mice).
NIMH-70	Utilization of space through time by rats in the activity alley.
NIMH-71	Visual discriminative processes in the pigeon.
NIMH-72	Discrimination learning in normal humans.
NIMH-73	Adaptive behavior of families to the hospitalization of the father for mental illness.
NIMH-74	The impact of mental illness upon the family.
NIMH-75	The adaptation of the mental patient to his family upon return from hospitalization.
NIMH-76	The impact upon the family of serious physical illness of one of the family members.
NIMH-77	Social, demographic, and health factors relating to mental illness in Washington County, Maryland.
NIMH-78	Social psychological factors in juvenile delinquency in a suburban area.
NIMH-79	The relationship between nurses' and aides' perceptions of given psychiatric patients and their functioning with these patients.
NIMH-80	Study of norms regulating interaction among patients and personnel on wards containing some psychotic patients.
NIMH-81	Life-styles in aging.
NIMH-82	A phenomenological study of child-patient behavior.
NIMH-83	Public reactions to the threat of polio in an epidemic area.
NIMH-84	Federal management intern career patterns.
NIMH-85	Social life of the mental hospital patient.
NIMH-86	A comparison of the social relationships of children in the middle and lower socio-economic strata.

Project No.	Project Title
NIMH-87	Nursing personnel's response to altering aspects of the traditional social structure on a mental hospital ward.
NIMH-88	The identification of self in identical quadruplets: A special case of the problems of sibling rivalry and of multiple status.
NIMH-89	The validity of retrospective data on parent-child relationships.
NIMH-90	Adult leadership in children's groups: A study of leader's sensitivity and functioning in relation to the social-cultural composition of the group.
NIMH-91	The formation of children's peer relationships.
NIMH-92	A twin family study of mental deficiency.
NIMH-93	Design, development, and construction activities.
NIMH-94	Repair, maintenance, and technical assistance.
NIMH-95	Consultation, internal operation, and administrative activities.
NINDB-1	Preparation of monograph "Regeneration in the Central Nervous System".
NINDB-2	Regeneration of the transected mammalian spinal cord.
NINDB-3	Effects of anoxia at birth on brain structure and function.
NINDB-4	Alterations in the brain with aging.
NINDB-5	Residual function after subtotal spinal cord transection in the cat.
NINDB-6	Development of fiber tracts and nuclei in the brain in human embryos.
NINDB-7	Relation of age to regeneration in stab wounds of the brain.
NINDB-8	Induction of tremor, rigidity, akinesia and related phenomena in laboratory animals by means of reserpine and other drugs.
NINDB-9	Stomach denervation in newborn guinea pigs and the learning of hunger.

Project No.	Project Title
NINDB-10	Stomach cues in hunger-thirst discrimination.
NINDB-11	The effects of stomach denervation and hypothalamic lesions on food consumption.
NINDB-12	Electron-micrographic exploration of brain structures and function.
NINDB-13	Development of new micromethods for determining pyridine nucleotide dependent enzymes in biological material.
NINDB-14	Electrophoretic patterns of tissue removed from various parts of the central nervous system.
NINDB-15	Quantitative histochemical studies of nervous tissue.
NINDB-16	Rate of regeneration in peripheral nerves.
NINDB-17	Neuronal specificity in the autonomic nervous system in mammals.
NINDB-18	Taste bud regeneration in the adult mammal.
NINDB-19	Comparative anatomical study of the area postrema of the brain.
NINDB-20	Hematological and vascular factors in cerebral siderosis.
NINDB-21	Volumetric studies on the mammalian spinal cord.
NINDB-22	Histochemical characteristics of the brain and spinal cord affected by anesthetics.
NINDB-23	Hemodynamic factors concerned with the formation of cerebral hemorrhages.
NINDB-24	Lipide histochemistry of the central nervous system.
NINDB-25	Lipide and lipoproteins of guinea pig brains.
NINDB-26	Origin and termination of the frontopontine tract.
NINDB-27	The precise termination of certain tracts and other connections of the brain stem and spinal cord.
NINDB-28	Autonomic innervation of the inner ear.

Project No.	Project Title
NINDB-29	The efferent or recurrent fibers of the central and peripheral auditory pathways in mammals.
NINDB-30	The role of the hypothalamus and other parts of the brain on temperature regulation.
NINDB-31	Role of the spinal cord in mechanisms of temperature regulation.
NINDB-32	The effect of the stimulation of and the effect of blood temperature of the hypothalamus in the regulation of body temperature.
NINDB-33	X-irradiation of the hypothalamus.
NINDB-34	The effect of the circulating titre of antidiuretic hormone on the release of this hormone from the neurophphpophysis.
NINDB-35	Vascular supply of the spinal cord.
NINDB-36	Relationship between neurosecretion and milk ejection.
NINDB-37	Ion permeabilities of nerve membranes. A. Experimental investigations of the squid giant axon.
NINDB-38	Ion permeabilities of nerve membranes. B. Theoretical investigations of the squid giant axon.
NINDB-39	Correlation of acetylcholinesterase inhibition spectrum with nerve action,
NINDB-40	Metabolism of derivatives of coenzyme A.
NINDB-41	Biosynthesis of fatty acids.
NINDB-42	Biosynthesis of cerebrosides..
NINDB-43	Effects of LSD on enzymatic reactions.
NINDB-44	Metabolism of inositol.
NINDB-45	The effect of intra-cellularly injected enzymes upon the impedance and action potential of the squid giant axon.
NINDB-46	The relationship of nucleotides to lipid synthesis.

Project No.	Project Title
NINDB-47	Toxicity of Neurophysiologically Active Chemicals.
NINDB-48	Studies on the process of action potential production.
NINDB-49	The parallelism between the action potential, action current, and membrane resistance at a node of Ranvier.
NINDB-50	Analysis of the action potential of the nerve cell body.
NINDB-51	Analysis of the sensory mechanism in the inner ear.
NINDB-52	Analysis of the changes in the duration of electric responses of single nerve fibers following repetitive stimulation.
NINDB-53	The effects of hydrostatic pressure and temperature on single nerve fiber activity.
NINDB-54	Origin of rhythmic activity in the spinal cord.
NINDB-55	Mechanisms of interaction between neurons in the spinal cord.

R.P.C. - 1

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Development and Regeneration
SECTION

4.
LOCATION

5. NINDB-1
SERIAL NO.

6. Preparation of monograph "Regeneration in the Central Nervous System"
PROJECT TITLE

7. W. F. Windle
PRINCIPAL INVESTIGATOR(S)

8. Secretarial and library personnel
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION.

Objectives: To edit and prepare for publication a monograph entitled "Regeneration in the Central Nervous System". To organize a "Conference on the Biology of Neuroglia" to be held under the auspices of the National Neurological Diseases and Blindness Advisory Council in March 1956.

Accomplishment: Publication: "Regeneration in the Central Nervous System", by 33 contributors; W. F. Windle, editor; Springfield, Ill., Charles C Thomas.

Proposed course of project: To continue work as indicated under "objectives".

R.P.C. - 2
December 1955 Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-1
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: Research

13. NO COOPERATING UNITS

14.

Honors, Awards, and Publications

16. PUBLICATIONS:

"Regeneration in the Central Nervous System", by 33 contributors; W. F. Windle, editor; Springfield, Ill., Charles C Thomas

17. NONE

R.P.C. - 1

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Development and Regeneration
SECTION

4.
LOCATION

5. NINDB -2
SERIAL NO.

6. Regeneration of the transected mammalian spinal cord.
PROJECT TITLE

7. W. F. Windle
PRINCIPAL INVESTIGATOR(S)

8. Junior personnel of section.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION.

Objectives: To bring about anatomical and physiological regeneration in the acutely transected spinal cord. To try to bring about functional restitution as a result of this regeneration.

Methods employed: The spinal cord of the adult cat or monkey is surgically transected at the lower thoracic or upper lumbar level. After this, extraordinary methods of animal care are necessary on a daily basis to maintain these spinal animals in first class condition. Certain pyrogenic bacterial polysaccharides are administered intravenously to inhibit formation of a glial barrier or, in other ways, to promote a condition favorable to regeneration of central nerve fibers across the transection site. As a rule two animals are operated at each session, one receiving no therapy and serving as a control for the other which is given the pyrogen. Comparison of the' subsequent events in respect to neurological improvements is made from time to time and recorded in 3-D motion pictures. Other drugs and hormonal agents are being used.

Major findings: Findings in the current series tend to be confirmatory of earlier experiments carried out prior to the establishment of the Laboratory of Neuroanatomical Sciences. One new observation: phenomena resembling those encountered in spinal cats receiving intravenous pyrogen therapy occurred in an animal which postoperatively contracted a urinary tract infection with an organism known to produce bacterial pyrogens. Experiments in African green monkeys have been completed and the following manuscript has been submitted to Publications and Reports for clearance: "Regeneration in the Cord of Spinal Monkeys" by W. F. Windle, Jae L. Littrell, J. O. Smart and Jane Joralemon". Two reviews are in process of being prepared for Physiological Reviews on the subjects: "Regeneration in the Central Nervous System" and "Regeneration in the Peripheral Nerves" by W. F. Windle and L. Guth.

NINDB-2
SERIAL NO.

Significance: The studies form a basis for possible therapy in acute human paraplegias. At the present time there is little other than physical rehabilitation that can be done for the patient with a severed spinal cord. If a way can be found to obtain even the least amount of regeneration in the human spinal cord, such as has been demonstrated in animals, the prognosis for the acute spinal cord injury patient should be improved.

Proposed course of project: It is planned to continue this project vigorously. More emphasis will be placed on an effort to re-establish function after spinal cord transection.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-2
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: Research

13. NO COOPERATING UNITS

14.

Honors, Awards, and Publications

16. PUBLICATIONS:

Clemente, C. D. and W. F. Windle, 1954. Regeneration of nerve fibers in the spinal cord of the adult cat, J. Comp. Neur., 101:601-732. (Dec.) 1954.

17. NONE

R.P.C.- 1
December 1955 Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Development and Regeneration
SECTION

4.
LOCATION

5. NINDB-3
SERIAL NO

6. Effects of anoxia at birth on brain structure and function.
PROJECT TITLE

7. W. F. Windle
PRINCIPAL INVESTIGATOR(S)

8. Jan H.W.Cammermeyer, C. J. Bailey and junior personnel.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION.

Objectives: In animals to simulate the abnormal neuromuscular behavior known in man as cerebral palsy. To determine effects of anoxia during birth on brain structure and on learning ability. Similarly, to determine effects of obstetrical anesthetic agents.

Methods employed: Experimental surgical approach in pregnant guinea pigs to asphyxiate the young; resuscitation of the newborn followed by study with methods of experimental neuropathology and experimental psychology.

Major findings: The staff for the research project has been recruited. A breeding colony of guinea pigs has been established. The experiments to date have not yet yielded information which can be reported.

The principal investigator presented lectures with motion picture demonstration on the subject: "Asphyxia Neonatorum in Relation to Brain Damage and Mental Retardation" at the following institutions:

Symposium on "Metabolic Aspects of Mental Deficiency" Milwaukee, Wisc., June 20, 1955.

San Patricia V.A. Hospital, San Juan, P.R., August 23, 1955.

Significance: The study should form a basis for understanding of the comparable human conditions. It should lead to recommendations concerning ways of preventing certain neurological disorders at birth.

Proposed course of project: It is planned to continue experiments begun by the principal investigator several years ago, to extend these and to supplement them with studies in other species of animals, notably primates. Progress has been made toward possible establishment of a study on monkeys in cooperation with scientists in another institution.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-3
SERIAL NO

11. BUDGET DATA:

12. BUDGET ACTIVITY: Research

13. NO COOPERATING UNITS

14.

Honors, Awards and Publications

16. PUBLICATIONS: NONE

17. NONE

R.P.C.- 1
December 1955 Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Development and Regeneration
SECTION

4.
LOCATION

5. NINDB-4
SERIAL NO.

6. Alterations in the brain with aging.
PROJECT TITLE

7. H. H. Wilcox (by contract)
PRINCIPAL INVESTIGATOR(S)

8. W. F. Windle (as consultant)
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION.

Objectives: To determine possible quantitative and qualitative changes which may occur in the brain with aging.

Methods employed: A series of healthy guinea pigs from a single breeding colony has been prepared for histological study by the perfusion-fixation and buffered thionine methods. The animals range in age from a few months to nearly 8 years (extremely old for this species).

Major findings: Preliminary study of this extensive series of specimens revealed development of pigmentation of larger neurons of the brain stem. There appeared to be no significant loss of cells nor loss of stainability of chromaphilic material in cells of the brain. Quantitative studies of the cerebellum showed a slight increase in number of Purkinje cells after 3 years of age. This may be related to changes in brain ground substance.

Significance: This is the first thorough study of material not subject to criticism on the basis of (1) complication by disease processes, (2) postmortem artefacts or (3) immersion-fixation artefacts.

Proposed course of project: The study under contract with the University of Tennessee will be pursued as vigorously as possible.

10. NINDB-4
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: Research

13. NO COOPERATING UNITS

14.

Honors, Awards, and Publications

16. PUBLICATIONS: None

17. NONE

R.P.C. - 1
December 1955 Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Development and Regeneration
SECTION

4.
LOCATION

5. NINDB-5
SERIAL NO.

6. Residual function after subtotal spinal cord transection in the cat.
PROJECT TITLE

7. W. F. Windle
PRINCIPAL INVESTIGATOR(S)

8. Junior personnel
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION.

Objectives: To produce subtotal transections of the spinal cord, leaving intact only a small number of nerve fibers in the ventral funiculi. To compare residual functional activities of such animals with activities acquired by animals in which total spinal cord transection had been followed by regeneration of nerve fibers induced by treatment with bacterial pyrogens.

Methods employed: In one series of cats, surgical dissection through the spinal cord at the level of the lower thoracic or upper lumbar region resulted in section of all nerve fibers except a few on either side of the median raphe in the ventral funiculi. In another series of cats, the cord was transected completely and therapy with various bacterial pyrogens instituted postoperatively. Observations were recorded in 3-D motion pictures.

Major findings: The animals with complete spinal cord transection exhibited no restitution of function during the period of the experiment. Animals with less than 5% of the white matter of the ventral funiculi remaining intact, have no retension of sensory modalities but have retained certain reflexes and motor functions, including some locomotion, comparable to animals of a previous series in which some regeneration in the spinal cord had taken place. Results were reported at the annual meeting of the American Association of Anatomists in Philadelphia in April 1955.

Significance: The experiments give a base against which to compare the early signs of regeneration in pyrogen treated spinal animals undergoing regeneration.

Proposed course of project: The project will terminate as soon as the histological part of the study is completed and results prepared for publication.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-5
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: Research

13. NO COOPERATING UNITS

14.

Honors, Awards, and Publications

16. PUBLICATIONS: None

17. NONE

R.P.C.- 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Development and Regeneration
SECTION

4.
LOCATION

5. NINDB-6
SERIAL NO.

6. Development of fiber tracts and nuclei in the brain in human embryos.
PROJECT TITLE

7. W. F. Windle
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION.

Objectives: To observe and describe the genesis and subsequent development of nerve fiber tracts and groups of nerve cells in the human brain and spinal cord.

Methods employed: The method of microscopical observation is employed in serial sections of the human embryos which have been collected during the past twenty years and prepared by certain silver staining methods to bring out finer details of neuron growth.

Major findings: A renewed study of the origin and migration of primary motor cell groups of the brain stem has shown that all visceral motor nuclei arise in a location adjacent to the floor plate of embryos 4-6mm long (end of the fourth week of gestation). These nuclei migrate to more lateral positions in embryos 12-14mm long (between the sixth and seventh weeks). This migration gives rise to the genu of the facial nerve and to similar bundles of fibers of much smaller size in the trigeminal, glossopharyngeal and vagus nerves.

Significance: Knowledge of intrinsic development of the human brain is fundamental to a clear understanding of adult brain anatomy and physiology. Little is known of intrinsic structural development at present.

Proposed course of project: The study of these human embryos will be continued throughout the coming year. It is hoped that additional human embryos can be obtained and subjected to silver staining.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-6
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: Research

13. NO COOPERATING UNITS

14.

Honors, Awards, and Publications

16. PUBLICATIONS: None

17. NONE

R.P.C.- 1
December 1955 Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Development and Regeneration
SECTION

4.
LOCATION

5. NINDB-7
SERIAL NO.

6. Relation of age to regeneration in stab wounds of the brain.
PROJECT TITLE

7. W. F. Windle
PRINCIPAL INVESTIGATOR(S)

8. Junior personnel
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION.

Objectives: To determine whether or not intracerebral nerve fibers can regenerate across a simple stab lesion in the brain in newborn and young kittens. To relate this to possible inhibition of glial barrier formation brought about by administration of bacterial pyrogens and other agents.

Methods employed: In kittens one hour to three weeks old, a simple stab wound into the cerebrum was inflicted under local anesthesia. Half of each litter received pyrogen therapy; half were controls. An attempt was made to keep the animals alive and in good health for a period of seventy days; some died earlier. The animals were killed by the perfusion fixation technique; the brains were dissected out and studied grossly; blocks of tissue at appropriate sites were removed and are being prepared by several neurological staining techniques.

Major findings: There appears to have been less adhesion formation in those kittens which had received pyrogen therapy. No microscopical findings are ready to report. An additional series of experiments is planned as soon as animals become available.

Significance: Whether or not regeneration in the mammalian central nervous system occurs more readily in the newborn and very young individual than in the adult is a moot question. The only investigation comparable to this one was carried out on rats in 1903, prior to the time when adequate neurological staining methods were available.

Proposed course of project: The course of the project will depend upon histological observations of the present series and availability of pregnant animals.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-7
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: Research

13. NO COOPERATING UNITS

14.

Honors, Awards, and Publications

16. PUBLICATIONS: None

17. NONE

R.P.C.- 1
December 1955 Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Development and Regeneration
SECTION

4.
LOCATION

5. NINDB-8
SERIAL NO

6. Induction of tremor, rigidity, akinesia and related phenomena in laboratory animals by means of reserpine and other drugs.
PROJECT TITLE

7. W. F. Windle
PRINCIPAL INVESTIGATOR(S)

8. J. Cammermeyer and junior personnel
OTHER INVESTIGATORS

9. **PROJECT DESCRIPTION.**

Objectives: To reproduce by means of drugs certain phenomena which manifest themselves in human subject in such disorders as paralysis agitans. To try to determine anatomical correlates of these phenomena. To explore means of alleviation of the symptoms.

Methods employed: Several mammals (opossum, mouse, rat, guinea pig, cat, African green monkey, chimpanzee) are being used. Exploratory experiments have been carried out with the following drugs: reserpine, chlorpromazine, "tremorine" (code name of new drug), harmine, harmaline and nicotine, administered acutely and chronically by various routes and in various doses. After chronic treatment with reserpine, animals are being sacrificed by the perfusion-fixation technique and their brains (and other organs) prepared for histological and histochemical studies. Experiments were recorded in 3-D motion pictures.

Major findings: Monkeys given reserpine orally in doses of 2.5 - 8.0 mg/kg showed (1) muscular rigidity of "cogwheel" type; (2) akinesia, torpor, catalepsy and lethargy; (3) tremor at rest which varied inversely with degree of lethargy (3 to 4 per second); (4) sialorrhea and other phenomena observed in human Parkinsonian patients.

Preliminary observations were presented at the September 1955, meeting of the American Physiological Society.

Significance: A method of reliably producing tremor in monkeys has been lacking. This technique provides a means of studying tremor and other phenomena.

Proposed course of project: Continuation of observations and extension of experiments. It is expected that Dr. Paul Glees of Oxford University will join the project as a visiting scientist next March.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-8
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: Research

13. NO COOPERATING UNITS

14.

Honors, Awards, and Publications

16. PUBLICATIONS: None

17. NONE

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Development and Regeneration
SECTION

4.
LOCATION

5. NINDB -9
SERIAL NO

6. Stomach denervation in newborn guinea pigs and the learning of hunger
PROJECT TITLE

7. C. J. Bailey
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To determine whether hunger is originally learned solely on the basis of cues from the stomach and whether denervation of the stomach before any eating has taken place will prevent this learning.

Methods employed: Surgical denervation of the stomachs of very young guinea pigs before they have had any experience of the reduction of hunger by eating. Comparison of the food consumption of such animals with that of guinea pigs which undergo a sham operation.

Significance: This experiment may provide information relevant to a clearer understanding of the mechanisms of hunger and information relevant to a controversy concerning the role of drives in learning.

Proposed course of project: To study the techniques involved in stomach surgery of newborn guinea pigs, sham operations and post-operative care such as tube feeding, and to collect data on the survival times of animals after operation.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-9
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: Research

13. NO COOPERATING UNITS

14.

Honors, Awards, and Publications

16. PUBLICATIONS: None

17. NONE

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Development and Regeneration
SECTION

4.
LOCATION

5. NINDB-10
SERIAL NO.

6. Stomach cues in hunger-thirst discrimination
PROJECT TITLE

7. C. J. Bailey
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To determine whether stomach distension cues can explain learning in a hunger-thirst discrimination in which there is no reinforcement with food or water.

Methods employed: A modification of the Skinner box is used to train rats to discriminate cues of hunger and thirst on the basis of a third drive. One response turns out a light if the animal is hungry and another if the animal is thirsty.

Major findings: Studies begun at Yale University indicate that, on one hand, hunger and thirst are each cues even when the responses are not reinforced with food or water, and on the other hand, that cues of stomach distension are not important when the responses are reinforced with food and water.

Significance: The proposed study should shed light on a theoretical controversy among psychological schools concerning the function of drives in learning.

Proposed course of project: After the learning described has taken place, tests like those described by Bailey and Porter, varying the fullness of the stomach independently of the need for food or water, will be given in order to find out which set of cues is functional in the original learning.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-10
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: Research

13. NO COOPERATING UNITS

14.

Honors, Awards, and Publications

16. PUBLICATIONS: None

17. NONE

R. P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Development and Regeneration
SECTION

4.
LOCATION

5. NINDB-11
SERIAL NO.

6. The effects of stomach denervation and hypothalamic lesions on food consumption
PROJECT TITLE

7. C. J. Bailey
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To study the effects of varying the order of two surgical procedures: denervation of the stomach and destruction of the ventromedial nucleus in rats. To determine whether hypothalamic obesity is due to changes in the stomach and whether the concomitant high food consumption can be learned so that it will continue after denervation of the stomach.

Methods employed: Electrolytic destruction of the ventromedial nucleus using a stereotaxic instrument, surgical denervation of the stomach, and careful measurements of food consumption.

Significance: This experiment should advance understanding of the mechanisms involved in hunger and, specifically, should determine the importance of cues from the stomach in the learning of hunger.

Proposed course of project: To work out techniques for denervation of the stomach and for stereotaxic destruction of the ventromedial nucleus. To start experimentation: the brain operation before the stomach in half the animals and the reverse order in the other, measuring food consumption after both operations.

R.P.C.-2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-11
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: Research

13. NO COOPERATING UNITS

14.

Honors, Awards, and Publications

16. PUBLICATIONS: None

17. NONE

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Neurocytology
SECTION

4.
LOCATION

5. NINDB-12
SERIAL NO.

6. Electron-micrographic exploration of brain structures and function
PROJECT TITLE

7. Chief, Section on Neurocytology, Sanford L. Palay, M. D. (at present holds appointment as consultant; will come on duty as soon as his laboratory is available).
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To conduct various studies of the ultrastructure of nerve cells, neuroglia, central synaptic mechanisms and peripheral nerve fiber terminations by the techniques of electron microscopy and micrography.

Methods employed: The electron microscope and other apparatus will be used to extend knowledge in the field of neurocytology.

Major findings: No report. Apparatus has been purchased but space for this project awaits completion of basement area of Bldg. 9.

Significance: The techniques employed in electron microscopy and other closely related techniques have undergone extensive development and perfection during the last two or three years. It is proposed to utilize these techniques in an exploratory manner in the Laboratory of Neuroanatomical Sciences. One cannot predict what may develop from this project. Personnel of a research unit, which will be formed, will collaborate with other investigators in the National Institute of Neurological Diseases and Blindness on related projects requiring investigation with the electron microscope.

Proposed course of project: To activate and extend the project in the coming months.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-12
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: Research

13. NO COOPERATING UNITS

14.

Honors, Awards, and Publications

16. PUBLICATIONS: None

17. None

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Neurocytology
SECTION

4.
LOCATION

5. NINDB-13
SERIAL NO.

6. Development of new micro methods for determining pyridine nucleotide dependent enzymes in biological material.
PROJECT TITLE

7. R. Wayne Albers
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To simplify procedures and make possible simultaneous analysis of large numbers of samples.

Methods employed: It has been found that as many as 50 samples can be incubated at one time and the reaction of the enzymes stopped by adding methyl cellosolve to each sample. After the samples have been sufficiently centrifuged to remove the precipitated protein, the reduced pyridine nucleotide may be measured at leisure by determining the optical density at 340 millimicrons.

Major findings: This method has been applied successfully to the measurement of glutomic, malic and isocitric dehydrogenoses. Its sensitivity has been considerably increased by a modification which permits the measurement of the fluorescence of the reduced nucleotides.

Significance: These methods will be used to extend the project on quantitative microbiochemistry of the nervous system.

Proposed course of project: It is proposed to develop a method for determining glycerophosphokinace, utilizing the above outlined technique.

R.P.C. - 2
December 1955 Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-13
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: Research

13. NO COOPERATING UNITS

14.

Honors, Awards, and Publications

16. PUBLICATIONS:

R. W. Albers and O. H. Lowry. Analytical Chemistry 27: 1829, 1955
"The Fluorimetric Determination of One Tenth to Ten Micrograms of Cholesterol"

17. NONE

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB INSTITUTE	2. Neuroanatomical Sciences LABORATORY	
3. Neurocytology SECTION	4. LOCATION	5. NINDB-14 SERIAL NO.

6. Electrophoretic patterns of tissue removed from various parts of the central nervous system.
PROJECT TITLE

7. R. Wayne Albers
PRINCIPAL INVESTIGATOR(S)

8. Milton W. Brightman
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To develop paper electrophoresis as a method complimentary to that outlined in the project on quantitative microbiochemical studies of nervous tissue (NINDB).

Methods employed: Paper electrophoresis and related techniques.

Major findings: This project has not been developed beyond what was previously reported.

Significance: This project should contribute basic knowledge in cytobiochemistry of the nervous system. The field is very new and largely unexplored.

Proposed course of project: It is proposed to use this technique in a study of some proteins found in certain areas of the hypothalamus if the results of another project appear to justify it.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-14
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: Research

13. NO COOPERATING UNITS

14.

Honors, Awards, and Publications

16. PUBLICATIONS: None

17. NONE

R.P.C. - 1 .
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Neurocytology
SECTION

4.
LOCATION

5. NINDB-15
SERIAL NO.

6. Quantitative histochemical studies of nervous tissue
PROJECT TITLE

7. R. Wayne Albers
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The ultimate objectives of these studies are (1) to establish the biochemical composition of the histologically distinct elements of the nervous system, and (2) to determine the manner in which these elements contribute to the biochemistry of neural function.

Methods employed: The principle methods are based upon those of Linderstrøm-Lang and of Lowry, which employ frozen-dried tissue sections for obtaining samples of relatively homogeneous cytological composition. Enzymatic activities and biochemical composition are but slightly altered from that of fresh tissue in most instances. Samples having a dry weight of .01-50 µg. may be subjected to a wide variety of analyses.

As a tool for the extension of these studies to the hypothalamic-hypophysial system, a sensitive method for bioassay of anti-diuretic activity is being developed in collaboration with Dr. M. W. Brightman.

Major findings: Preliminary to the histochemical study of the visual system in the cat, the kinetic properties of several enzymes of whole homogenate of cat brain have been investigated. Some of these findings are described below. The enzyme activities are reported in terms of millimicromoles of substrate transformed per microgram of tissue and per hour.

Glutamic dehydrogenase: This enzyme loses activity rapidly even at room temperature. Consequently the incubations have been carried out at 18°C. At this temperature and pH 8.1, the activity is 0.05. This is consonant with the value reported for rabbit brain.

6-Phosphogluconic acid dehydrogenase: At 38°, pH 8.7, this activity is 0.12, almost identical with that for rat and rabbit brains. The optimal pH for the cat brain enzyme is 8.7. The temperature coefficient is 1.9. The linearity of the reaction with time is improved in the presence of 0.005 M adenosine-5-phosphate. Possibly there is a triphosphopyridine nucleotidase in cat brain which is inhibited by the adenylic acid. When the dehydrogenase is partially purified by ammonium sulfate fractionation and added back to the crude homogenate, no inhibition of the expected additive activity is observed.

Malic dehydrogenase: The activity of whole cat brain malic dehydrogenase is 15.6 at 38° and pH 10.5. The enzyme is stable at dilutions of 1:100,000 for 2 hours in the incubation medium containing 1% bovine albumin.

Iso-citric dehydrogenase: The enzyme activity is about 0.05 at 23°. The optimum pH is 7.5.

Aldolase: The enzymatic activity of whole homogenate is about 0.62 at 38°. The optimum pH is 8.2. However, the enzyme is considerably more stable in less alkaline media.

Significance: This project should contribute to our basic knowledge of the histochemistry of the nervous system. The data in this field is rudimentary at the present time.

Proposed course of project: The visual system of the cat has been selected for one phase of this study. The techniques outlined above will be applied to the lateral geniculate and superior collicular nuclei, the visual cortex and some of the associated fiber tracts. It is proposed, in addition, to study the comparative biochemistry of the degenerated tracts and nuclei which result from ablation of the visual cortex and severance of the optic tract. The resulting loss of neurons and proliferation of glial elements should result in corresponding changes in the biochemical composition of the tissue.

The perfection of the bioassay for anti-diuretic activity will be followed by its use in conjunction with other micro-analytical techniques to seek a correlation between the neuro-endocrine function of certain hypothalamic areas and other biochemical processes.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-15
SERIAL NO

11. BUDGET DATA:

12. BUDGET ACTIVITY: Research

13. NO COOPERATING UNITS

14.

Honors, Awards and Publications

16. PUBLICATIONS: NONE

17. NONE

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Neurocytology
SECTION

4.
LOCATION

5. NINDB-16
SERIAL NO.

6. Rate of regeneration in peripheral nerves
PROJECT TITLE

7. Lloyd Guth
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To review the subject of nerve regeneration and initiate a study on rate of nerve regeneration.

Methods employed: (a) Extensive review of literature on nerve regeneration was made. (b) Longitudinal sections of rat sciatic nerve were prepared at daily intervals after crush by the protargol technique. Examination of sections for distance travelled by fastest regenerating fibers was attempted.

Major findings: (a) A review article of approximately 40 pages in length and containing about 400 references is in preparation. Completion of the manuscript in 2 months with subsequent publication in Physiological Review is contemplated. (b) Protargol staining is inadequate for this study as difficulty of differentiating connective tissue elements from regenerating nerve fibers is too difficult. Also it was found that strong nerve crush does not necessarily destroy all nerve fibers.

Significance: An adequate review of the literature on nerve regeneration has not appeared since 1942, and need for a more recent comprehensive survey of the field exists. A purely anatomical study on the rate of nerve regeneration has not been undertaken even though as long ago as 1928 Cajal declared the need for such a study.

Proposed course of project: (a) Completion and publication of review article within the year. (b) Methylene blue technique for selective axon staining will be attempted on sectioned rather than crushed nerves. Distances travelled by fastest growing axons to be measured.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. **NINDB-16**
SERIAL NO

11. BUDGET DATA:

12. BUDGET ACTIVITY: Research

13. NO COOPERATING UNITS

14.

Honors, Awards and Publications

16. PUBLICATIONS: NONE

17. NONE

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Neurocytology
SECTION

4.
LOCATION

5. NINDB-17
SERIAL NO.

6. Neuronal specificity in the autonomic nervous system in mammals
PROJECT TITLE

7. Lloyd Guth
PRINCIPAL INVESTIGATOR(S)

8. Junior Personnel
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To determine whether or not end-organ induction of neuronal specificity occurs in the mammalian autonomic nervous system.

Methods employed: Vago-sympathetic anastamosis was performed in cats in fashion as to allow regenerating vagal fibres to enter the superior cervical sympathetic ganglion. Auricular vasomotor and pupillary reflexes were studied.

Major findings: It has been confirmed that vasomotor responses (as measured by ear temperature changes) return to normal after regeneration of the vagus nerve. The pupil does not show any such complete functional restitution, but responds, rather, to stimuli normally evoking vagal discharge such as those related to food and hunger.

Significance: No other adequately-controlled demonstrations of functional return in mammals after heterogeneous nerve anastamosis are known to exist.

Proposed course of project: By means of more direct measures of auricular blood flow (a measure independent of environmental temperature) we will be able to ascertain whether or not this return of vasomotor tone occurred because of alteration in specificity and central synaptic relationships of the vagus nerve. Use of a densitometer for this purpose has been attempted successfully in normal and sympathectomized cats and will be applied to animals having vago-sympathetic anastamosis.

R.P.C. - 2
December 1955 Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-17
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: Research

13. NO COOPERATING UNITS

14.

Honors, Awards, and Publications

16. PUBLICATION:

L. Guth. Functional Recovery after vago-sympathetic anastamosis in the cat, Am. J. Physiol. (In Press)

17. NONE

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Neurocytology
SECTION

4.
LOCATION

5. NINDB-18
SERIAL NO.

6. Taste bud regeneration in the adult mammal
PROJECT TITLE

7. Lloyd Guth
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To determine the mechanism by which adult taste buds disappear when denervated and reappear when reinnervated.

Methods employed: (a) Quantitative histopathological study of taste bud degeneration in the rat. (b) Heterogeneous reinnervation of taste buds in the cat. (c) Transplantation of lingual epithelium to other regions of the body in inbred mice.

Major findings: Preliminary data suggests that foreign nerves are equally capable of initiating taste bud regeneration as are gustatory nerves. Collaboration on this project with Dr. L. B. Arey of Northwestern University has begun.

Significance: The proposed experiments (a, b and c) will determine whether taste bud regeneration is a process of differentiation from normal lingual epithelium under inductive neural influences. The existence of field effects will also be noted. This may help enable us to ascertain the agents responsible for induction, differentiation and field effects as revealed previously by the techniques of experimental embryology. The fetal mammal is too resistant to experimental manipulation for use in such studies.

Proposed course of project: (1) The sequence of degenerative changes in the circumvallate papilla of the rat following section of the glossopharyngeal nerves is to be determined. (2) Further experiments on heterogeneous reinnervation of taste buds will be performed to determine conclusively whether foreign nerves can restore and maintain taste buds in the circumvallate papillae of the cat.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-18
SERIAL NO

11. BUDGET DATA:

12. BUDGET ACTIVITY:Research

13. NO COOPERATING UNITS

14.

Honors, Awards and Publications

16. PUBLICATIONS: NONE

17. NONE

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Experimental Neuropathology
SECTION

4.
LOCATION

5. NINDB-19
SERIAL NO.

6. Comparative anatomical study of the area postrema of the brain
PROJECT TITLE

7. Jan Cammermeyer
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION.

Objectives: To discover the nature and function of certain cells which are peculiar to the area postrema of the brain.

Methods employed: Conventional cytological techniques are used to study this region in several species of animals.

Major findings: Its relative size and extent over the floor of the fourth ventricle varies greatly (the area postrema of the squirrel is remarkably large). Species differences were noted in certain histochemical qualities of the area postrema. The principal cells have the same structural appearance in all species studied but it is noteworthy that in man they differ from those in all other animals studied, inasmuch as they contain a melanin-like pigment.

Significance: Results of this research should contribute to our knowledge of the control of blood flow through the vasculature of the medulla oblongata (through a possible neurosecretory function of the area postrema cells) and of the formation of the cerebrospinal fluid (through diffusion of substances from the vessels of the area postrema).

Proposed course of project: This project has been temporarily discontinued in order to activate other projects that at the present time were felt to have greater immediate importance.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-19
SERIAL NO

11. BUDGET DATA:

12. BUDGET ACTIVITY: Research

13. NO COOPERATING UNITS

14.

Honors, Awards and Publications

16. PUBLICATIONS: NONE

17. NONE

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Experimental Neuropathology
SECTION

4.
LOCATION

5. NINDB-20
SERIAL NO.

6. Hematological and vascular factors in cerebral siderosis
PROJECT TITLE

7. Jan Cammermeyer
PRINCIPAL INVESTIGATOR(S)

8. Helen Ramsey
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION.

Objectives: To determine possible sources of siderosis in the brain, other than from destruction of blood hemoglobin.

Methods employed: Histological methods applied to material from experiments on animals. The animals have been subject to fat embolism and sections from organs and brain have been prepared for the study of excess deposition of iron in the tissues.

Major findings: Excessive amounts of iron are found in visceral organs of animals subjected to experimental fat embolism. Some discrete amount of iron occurs within areas of acute brain necrosis.

Significance: The extra deposition of iron in acute experiments may indicate that siderosis is due to some hitherto unknown factors active in the general iron metabolism.

Proposed course of project: To utilize animals of different species and age and kept under different diets.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. **NINDB-20**
SERIAL NO

11. BUDGET DATA:

12. BUDGET ACTIVITY:Research

13. NO COOPERATING UNITS

14.

Honors, Awards, and Publications

16. PUBLICATIONS: NONE

17. NONE

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Experimental Neuropathology
SECTION

4.
LOCATION

5. NINDB-21
SERIAL NO.

6. Volumetric studies on the mammalian spinal cord
PROJECT TITLE

7. Jan Cammermeyer
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION.

Objectives: To determine physical and anatomical properties of the spinal cord that support blood flow and prevent development of edema in different normal animals.

Methods employed: Dog, cat, rabbit and opossum have been utilized. The volume of the spinal cord has been determined in normal animals and after exposure of the spinal cord to water and fixatives.

Major findings: The reaction of the spinal cord which has been submerged in water varies with the weight of the animal and with this species from which the cord was taken. The volumetric proportions of the spinal cord are normally retained when the animals have been prepared according to perfusion technique slightly modified from the one proposed by Koenig, Groat and Windle.

Significance: To collect enough experimental data that will make it possible to determine whether the volume has been affected or has remained intact following experiments on the spinal cord.

Proposed course of project: Continue the study with (1) observations on other species (dog, sheep, monkey, etc), (2) histological survey of the material, (3) comparison of the obtained results with those of planigraphic measurements, and (4) to apply the same techniques to animals subjected to trauma, compression ischemia, aortic occlusion ischemia of the spinal cord, forced activity in tread mill, changes in dietary regimen, etc.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-21
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY:Research

13. NO COOPERATING UNITS

14.

Honors, Awards, and Publications

16. PUBLICATION:

17. NONE

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Experimental Neuropathology
SECTION

4.
LOCATION

5. NINDB-22
SERIAL NO.

6. Histochemical characteristics of the brain and spinal cord affected by anesthetics.
PROJECT TITLE

7. Jan Cammermeyer
PRINCIPAL INVESTIGATOR(S)

8. Helen Ramsey
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION.

Objectives: To determine the sequence of histochemical changes of the nerve cells within the spinal cord following the administration of anesthetic agents.

Methods employed: In cats and dogs the spinal cord has been removed after specified time and the volume of the spinal cord has been determined. These specimens have been prepared for the usual histological preparation. Histochemical techniques will be adopted later.

Major findings: After severe anesthesia the spinal cord shows changes in volumetric proportions.

Significance: These observations on the changed volumetric proportions may help understand the mechanism underlying delayed changes in histochemical activity of the nervous tissue and may provide some information about physical changes taking place after prolonged anesthesia.

Proposed course of project: To determine the cause of the volumetric changes observed, the histological appearance and histochemical activity.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-22
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY:Research

13. NO COOPERATING UNITS

14.

Honors, Awards, and Publications

16. PUBLICATION:

17. NONE

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Experimental Neuropathology
SECTION

4.
LOCATION

5. NINDB-23
SERIAL NO.

6. Hemodynamic factors concerned with the formation of cerebral hemorrhages
PROJECT TITLE

7. Jan Cammermeyer
PRINCIPAL INVESTIGATOR(S)

8. Helen Ramsey
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION.

Objectives: To determine the ways in which petechial hemorrhages occur in cerebral tissue.

Methods employed: A preliminary survey is made on material from mouse, rat, guinea pigs and rabbit. These animals subjected to experimental fat embolism have been sacrificed after varying length of time. The histological study will be supplemented with direct physiological survey of hemodynamic properties of cerebral vessels.

Major findings: Petechial hemorrhages are noticed in white and gray matter. They occur scattered free in the tissue and adjacent to minute necrosis.

Significance: The collection of histological material from animals treated by different experimental procedures will help understand the factors that govern the formation of hemorrhages and to determine if the same factors are active to the same degree in different species.

Proposed course of project: To utilize more species and other necrotizing agents in order to find factors that dispose for pathological changes and may contribute to differences in mode of tissue reaction.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-23
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY:Research

13. NO COOPERATING UNITS

14.

Honors, Awards, and Publications

16. PUBLICATION:

17. NONE

R.P.C.- 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Experimental Neuropathology
SECTION

4.
LOCATION

5. NINDB -24
SERIAL NO.

6. Lipide histochemistry of the central nervous system.
PROJECT TITLE

7. M. H. Hack
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION.

Objectives: To study the lipide histochemistry of the central nervous system.

Methods employed: Application of freeze-drying techniques to lipide histochemistry some new techniques will have to be developed in order to examine for a variety of lipides.

Major findings: Direct treatment of frozen dried brain sections (from cryostat) by reagents for visualizing acetal lipides has produced satisfying results.

Significance: Our studies are directed toward providing basic data which can be used as a base line for evaluation of later work on "palsied" guinea pigs.

Proposed course of project: This project is just barely under way and should continue as initiated.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-24
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: Research

13. NO COOPERATING UNITS

14.

Honors, Awards, and Publications

16. PUBLICATION:

17. NONE

R.P.C.- 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Experimental Neuropathology
SECTION

4.
LOCATION

5. NINDB-25
SERIAL NO.

6. Lipide and lipoproteins of guinea pig brains.
PROJECT TITLE

7. M. H. Hack
PRINCIPAL INVESTIGATOR(S)

8. Junior personnel
OTHER INVESTIGATOR(S)

9. PROJECT DESCRIPTION.

Objectives: To study the lipide and lipoprotein composition of the brain of guinea pig primarily during neonatal growth.

Methods employed: Preparation of extracts and chemical assay of these extracts by various procedures, some new techniques are being developed in order to obtain more accurate quantitative data.

Major findings: Too few assays have been completed to report.

Significance: Our studies are directed toward providing basic data which can be used as a base line for evaluation of later work on "palsied" guinea pigs.

Proposed course of project: This project is just barely under way and should continue as initiated.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-25
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY:Research

13. NO COOPERATING UNITS

14.

Honors, Awards, and Publications

16. PUBLICATIONS:

17. NONE

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Functional Neuroanatomy
SECTION

4.
LOCATION

5. NINDB-26
SERIAL NO.

6. Origin and termination of the frontopontine tract.
PROJECT TITLE

7. Grant L. Rasmussen
PRINCIPAL INVESTIGATOR(S)

8. Junior Personnel
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: (a) To determine whether or not the frontopontine tract possesses fibers of sub-cortical origin. (b) To trace fiber components to termination in pons and elsewhere.

Methods employed: Performance of total and subtotal hemispherectomies in monkeys and other species of animals; placement of lesions in the cerebral peduncle; determination of the origin, course and endings of the fibers by means of suitable neuropathological techniques.

Major findings: Preliminary studies in material taken from human hemispherectomy cases suggest a sub-cortical origin of numerous thinly myelinated fibers of this tract. No progress made during past year due to lack of suitable human material, macaque monkeys and lack of time to devote to this project.

Significance: Observations resulting from this project should (a) add to our knowledge regarding the origin and termination of this tract; (b) form a basis for subsequent physiological studies of its function and (c) lead to an understanding of the results obtained in humans after section of the frontopontine tract as is practiced in certain neurological procedures.

Proposed course of project: To continue and extend this study particularly on primates and additional human hemispherectomy cases that might be obtained throughout the coming year. It should be noted that other fiber tracts connecting the cerebral cortex and lower centers will be investigated by similar methods as time, personnel and facilities permit.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-26
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY:Research

13. NO COOPERATING UNITS

14.

Honors, Awards, and Publications

16. PUBLICATION:

17. NONE

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Functional Neuroanatomy
SECTION

4.
LOCATION

5. NINDB-27
SERIAL NO.

6. The precise termination of certain tracts and other connections of the brain stem and spinal cord.
PROJECT TITLE

7. Grant L. Rasmussen
PRINCIPAL INVESTIGATOR(S)

8. Junior Personnel
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To determine the synaptic connections of certain fiber tracts and cranial nerve afferents of the brain stem and spinal cord. The study includes afferent terminals of the auditory, vestibular and reticular nuclei and certain afferent and efferent connections of the spinal cord nuclei.

Methods employed: Production of lesions surgically at appropriate places in the peripheral and central nervous system of cats and other mammals, following the course of axonal degeneration by the Nauta technique and terminal degeneration by a method recently developed in the laboratory which accomplishes complete and selective impregnation of various types of terminals.

Major findings: During the past year considerable time has been expended toward development of adequate technics for demonstrating various types of synaptic endings in order to demonstrate experimentally by histological means the precise interneuronal connections under study. Previously no adequate method has been available for this purpose. Finally, the necessary efficacious technique has been developed which reveals the various types of terminals in a complete and a remarkably clear cut fashion. Due to the high selectivity of the techniques all endings stand out in sharp relief against a lightly colored background of cell bodies and fibers; a condition which is ideal for studying qualitative and quanitative histopathological changes of the synaptic endings following Wallerian degeneration. The method has been tested under various experimental conditions with good results.

Significance: Exact knowledge of neuronal connections in most parts of the central nervous system is almost completely lacking, due chiefly to inadequate methods for studying neuronal connections. The new degeneration technique offers an effective means of revealing information that is basic to the understanding of normal behavior and of neurological disorders.

Proposed course of project: To continue this project and to expand it with the help of one or more additional scientists.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-27
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: Research

13. NO COOPERATING UNITS

14.

Honors, Awards, and Publications

16. PUBLICATIONS:

17. NONE

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Functional Neuroanatomy
SECTION

4.
LOCATION

5. NINDB -28
SERIAL NO.

6. Autonomic innervation of the inner ear
PROJECT TITLE

7. Grant L. Rasmussen
PRINCIPAL INVESTIGATOR(S)

8. Junior Personnel
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To discover the origin and pathways of the autonomic fibers innervating the inner ear; particularly the sympathetic component.

Methods employed: Methods of experimental surgery in cats followed by degeneration of nerve fibers detected by special neurological techniques. Neurophysiological methods will also be employed.

Major findings: Certain routes postulated by otologists for fibers to reach the inner ear have been explored with, as yet, negative results. Histological preparations of experimental animal material is too incomplete at the present to permit disclosure of significant findings.

Significance: It is generally assumed that the autonomic system should play an important role in the proper functioning of the hearing and equilibratory organs. The delicate pressure balance between the endolymphatic and perilymphatic fluid systems is maintained in a large measure by the influence of secretory fibers and the vasomotor control is presumably mediated by sympathetic nerves. Vasomotor disturbance of the labyrinthe arteries is thought by many otologists to be responsible for tinnitus and equilibratory disturbances and that unequal pressures of the endo- and perilymph results in a condition known as "hydrops". This causes hearing and equilibratory disturbance (Menière's disease). Design of critical physiological experiments for testing the functional role of autonomic nerves is dependent on knowledge of the the precise origin course and termination of nervous components involved.

Proposed course of project: To study experimental material when histological preparations are prepared and to continue this study, if necessary, with exploration of all possible routes. Extension of this study to monkeys which has not been done thus far.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-28
SERIAL NO

11. BUDGET DATA

12. BUDGET ACTIVITY: Research

13. NO COOPERATING UNITS

14.

Honors, Awards and Publications

16. PUBLICATIONS: NONE

17. NONE

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Functional Neuroanatomy
SECTION

4.
LOCATION

5. NINDB-29
SERIAL NO.

6. The efferent or recurrent fibers of the central and peripheral auditory pathways in mammals.
PROJECT TITLE

7. Grant L. Rasmussen
PRINCIPAL INVESTIGATOR(S)

8. Junior Personnel
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION.

Objectives: To trace the course and establish the connections of chains of neurons from the cerebral cortex to the cochlea.

Methods employed: Placement of lesions surgically in cats and monkeys, subsequently following intrinsic degeneration of axons and their terminations by means of the Nauta axonal degeneration method and fiber terminals by means of a technique developed in this laboratory during the past year.

Major findings: This project is a continuation of a study carried out by the responsible investigator while at the University of Buffalo School of Medicine, sponsored there by O.N.R. It has revealed indications of an orderly system of connecting neurons conducting impulses from the auditory cortex to the cochlea, or organ of hearing. The histological preparations of the experimental animals used during the past year is too incomplete at the present time to permit report on this project.

Significance: Establishment of the presence of efferent fibers in a sensory nerve such as that of hearing, is a new discovery. This system evidently represents an auditory feedback mechanism. Electrophysiological studies, being carried on in collaboration with Dr. Galambos at Walter Reed Hospital, indicate that these efferent fibers have inhibitory or suppressor effects upon the afferent cochlea nervous activity.

Proposed course of project: Important anatomical details remain to be worked out using the newly developed method for demonstrating terminal degeneration. Correlations remain to be drawn with electrophysiological studies carried on with Dr. Galambos of Walter Reed, Dept. of Neurophysiology.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-29
SERIAL NO

11. BUDGET DATA

12. BUDGET ACTIVITY: Research

13. NO COOPERATING UNITS

14.

Honors, Awards and Publications

16. PUBLICATIONS: NONE

17. NONE

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Functional Neuroanatomy
SECTION

4.
LOCATION

5. NINDB-30
SERIAL NO.

6. The role of the hypothalamus and other parts of the brain on temperature regulation
PROJECT TITLE

7. Leo C. Massopust, Jr.
PRINCIPAL INVESTIGATOR(S)

8. Junior Personnel
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION.

Objectives: To determine the effects of placing lesions in various areas of the brain on temperature regulation.

Methods employed: During 1955 a specially designed and constructed stereotaxic instrument was developed for use with small laboratory animals for the placement of lesions within the brains by means of small electrodes. It was found that existing power sources gave lesions of large size and were difficult to control, thus a high frequency R.F. coagulator was developed for small and highly controllable bilateral lesions. Further, methods for taking simultaneous skin, brain and body temperatures were developed and tested.

Major findings: In order to place electrodes within the brains of small animals stereotaxic coordinates would have to be established. It was found that atlases of small laboratory animals containing these coordinates were non-existant, therefore, under this project such a coordinate atlas of the rat is being developed. It was obvious after measurements were made of histological sections of some 30 brains, that the skull size and brain size became progressively larger as the rats became heavier. Because of this it became necessary to construct three sets of coordinates for weight ranges of 100, 200 and 300 grams in the rat. This atlas is nearing completion.

Significance: Previously it has been shown that bilateral destruction of certain areas of the hypothalamus impaired the ability of the animal to maintain its temperature regulatory ability. There also was noted changes in oxygen consumption with certain lesions in the hypothalamus. Rats became obese, sham rage and altered estrus cycles appeared in other rats with hypothalamic lesions. The above mentioned lesions were large and too widespread to make any evaluations on pathways concerned with the above functions.

NINDB-30
SERIAL NO.

Proposed course of project: Continuation of the studies outlined above, the placement of more discrete lesions in areas leading to the hypothalamus, placement of more discrete lesions in areas leading away from the hypothalamus including the spinal cord, tracing pathways involved.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-30
SERIAL NO

11. BUDGET DATA

12. BUDGET ACTIVITY: Research

13. NO COOPERATING UNITS

14.

Honors, Awards and Publications

16. PUBLICATIONS: NONE

17. NONE

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Functional Neuroanatomy
SECTION

4.
LOCATION

5. NINDB -31
SERIAL NO.

6. Role of the spinal cord in mechanisms of temperature regulation
PROJECT TITLE

7. Leo C. Massopust, Jr.
PRINCIPAL INVESTIGATOR(S)

8. Junior Personnel
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To determine the role played by the spinal cord in temperature regulation, the pathways involved in temperature regulation, how the autonomic afferent and efferent pathways in the spinal cord affect temperature regulation and the type of receptors activating the temperature regulation mechanisms.

Methods employed: Gross interruption of fiber tracts in the various funiculi at cervical levels of the spinal cord, selective interruption of fiber tracts by means of a stereotaxic instrument, the tracing of these pathways into the brain stem by physiological and morphological means, the determination of the effect of spinal cord lesions on heat loss, heat conservation and heat production.

Major findings: Lesions were placed at C5-C7 of the spinal cord in about 60 rats. Animals, on histological examination, having total or subtotal transections were found to have a definite impairment of temperature regulation. Those animals having dorsal or ventral hemisections or medial cord lesions or right or left lateral hemisections showed no impairment of temperature regulation ability. However, rats with their lateral funiculi interrupted on both sides showed definite impairment of temperature regulation ability. This indicates the pathways important to the regulation of body temperature lie in the lateral funiculi in the rat.

Significance: This project will provide basic information on the significance of the intact spinal cord in temperature regulation, how the voluntary musculature is involved in heat production, how thermo-receptors activate the central mechanisms of temperature regulation, and a better understanding of the mechanisms involved in fever, shivering, panting and basic metabolic rate.

NINDB-31
SERIAL NO.

Proposed course of the Project: To place more discrete lesions, by means of stereotaxic methods into the lateral funiculi bilaterally and brain stem to determine the specific pathway or pathways involved in maintaining the body temperature, the effect of various stresses on the efficiency of the thermoregulatory mechanisms, how the loss of certain pathways and areas of the brain control or integrate the whole mechanism of homeostasis.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-31
SERIAL NO

11. BUDGET DATA

12. BUDGET ACTIVITY: Research

13. NO COOPERATING UNITS

14.

Honors, Awards and Publications

16. PUBLICATIONS: NONE

17. NONE

R. P. C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Functional Neuroanatomy
SECTION

4.
LOCATION

5. NINDB-32
SERIAL NO.

6. The effect of the stimulation of and the effect of blood temperature of the hypothalamus in the regulation of body temperature
PROJECT TITLE

7. Leo C. Massopust, Jr.
PRINCIPAL INVESTIGATOR(S)

8. Junior Personnel
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION.

Objectives: (a) To determine the effect of the temperature of the blood entering the hypothalamus on temperature regulation. (b) To stimulate various areas of the hypothalamus and determine the effects of such stimulation on temperature regulation.

Methods employed: In anesthetized cats the common carotids were exteriorized and cannulated with polyethylene tubing after heparin injection, the blood entering the heads of these animals through the tubing was cooled and heated by placing a loop of the tubing in water baths, stimulation electrodes were imbedded bilaterally in the hypothalamus and simultaneous records were taken of skin, brain and body temperatures. After 6 hour runs the animals were sacrificed by perfusion and their brains examined.

Major findings: After parameters of stimulation currents and blood heating and cooling were determined, baselines of brain skin and body temperatures were established in some 15 cats. Preliminary data indicates that the anterior hypothalamus when stimulated while warm blood is flowing through it, prevents the natural rise in rectal, skin and brain temperatures observed in control cats. Stimulation of the preoptic area and basal parts of the frontal lobes also prevents the above rises in temperature. However, this stimulation has no effect on the above temperatures when the blood entering the hypothalamus is cooled.

Significance: The project will provide basic information concerning heat production, heat loss, the activation of temperature control mechanisms, significance of the circulation in temperature regulation, and the mechanisms of fever.

NINDB-32
SERIAL NO.

Proposed course of project: To continue the above studies and extend these observations to other parts of the hypothalamus, brain stem, cortex and spinal cord, to determine what effect hypothalamic and other lesions have on brain, skin and body temperature when the carotid blood is heated and cooled.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-32
SERIAL NO

11. BUDGET DATA

12. BUDGET ACTIVITY: Research

13. NO COOPERATING UNITS

14.

Honors, Awards and Publications

16. PUBLICATIONS: NONE

17. NONE

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Functional Neuroanatomy
SECTION

4.
LOCATION

5. NINDB-33
SERIAL NO.

6. X-Irradiation of the hypothalamus.
PROJECT TITLE

7. Milton W. Brightman
PRINCIPAL INVESTIGATOR(S)

8. Junior personnel
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION.

Objectives: 1. A new method of producing selective lesions of the supraoptic and paraventricular nuclei of the hypothalamus.

2. To determine whether increased metabolic activity of neuroendocrine cells enhance their susceptibility to X-irradiation.

Methods employed: One group of rats has been given water and another group hypertonic solutions, and irradiated with varying dosages of x-rays. The water intake and urine output have been followed and several brains are being prepared for histological examination.

Major findings: To date, no diabetes insipidus has appeared. Several rats, however, have become blind.

Significance: This procedure may provide a new method of producing selective lesions in the neurosecretory nuclei with minimum injury to adjacent neurones.

This experiment may be the first to show that increased synthetic activity of neuroendocrine cells results in an increased susceptibility to irradiation injury.

Proposed course of project: Additional animals for each group are being prepared.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. **NINDB-33**
SERIAL NO

11. BUDGET DATA

12. BUDGET ACTIVITY: Research

13. NO COOPERATING UNITS

14.

Honors, Awards and Publications

16. PUBLICATIONS: NONE

17. NONE

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Functional Neuroanatomy
SECTION

4.
LOCATION

5. NINDB -34
SERIAL NO.

6. The effect of the circulating titre of antidiuretic hormone on the release of this hormone from the neurohypophysis.
PROJECT TITLE

7. Milton W. Brightman
PRINCIPAL INVESTIGATOR(S)

8. Dr. W. Albers and Junior personnel
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION.

Objectives: To determine whether circulating levels of posterior lobe hormones exert an effect on the output of these hormones and of neurosecretory material from the neurohypophysis.

Methods employed: In order to determine whether any release of hormone occurs, a suitable bioassay is necessary. In conjunction with Dr. W. Albers, a sensitive bioassay of antidiuretic hormone is being developed.

Major findings: Our bioassay is comparable to the most sensitive ones in use. It differs from existing methods in that a number of assays can be carried out on a single rat, involving a modicum of trauma and anesthesia.

Significance: A relatively simple, sensitive and rapid bioassay for A.D.H. is being developed.

Proposed course of project: This bioassay will enable both histological and pharmacological studies to be carried out on the neurohypophysis of a single rat subjected to appropriate experimental conditions.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-34
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: Research

13. NO COOPERATING UNITS

14.

Honors, Awards, and Publications

16. PUBLICATIONS:

17. NONE

R.P.C. - 1
December 1955 Analysis of NIH Program Activities

Project Description Sheet

1. NINDB INSTITUTE	2. Neuroanatomical Sciences LABORATORY

3. Functional Neuroanatomy SECTION	4. LOCATION	5. NINDB -35 SERIAL NO.

6. Vascular supply of the spinal cord.
PROJECT TITLE

7. Milton W. Brightman
PRINCIPAL INVESTIGATOR(S)

8. Junior personnel
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION.

Objectives: To determine the extrinsic and intrinsic vascular supply of the spinal cord of the cat.

Methods employed: A simplified India-ink-gelatin-formalin perfusion technique has been used to inject the entire vascular bed. Arteries and veins were differentiated by a second method involving a gelatin-corn-starch medium developed with iodine.

Major findings: The vascular pattern of the cat's cord demonstrates the free anastamoses between dorsal and ventral trunks. In contrast to man and the monkey, no great radicular artery supplies the lumbo-sacral segments. The comparatively highly vascular dura mater is in striking contrast to that of other species.

Significance: The sparing of the radicular vessels with their ascending and descending tributaries, and the extensive venous drainage of the dura, are important anatomical factors to be considered in any experimental manipulation of the cord.

Proposed course of project: The study has been extended to the rat, mouse, and shrew in which a great radicular vessel in the anterior lumbar region is a characteristic finding. The investigation on the cat is being prepared for publication.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-35
SERIAL NO

11. BUDGET DATA

12. BUDGET ACTIVITY: Research

13. NO COOPERATING UNITS

14.

Honors, Awards and Publications

16. PUBLICATIONS: NONE

17. NONE

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. NINDB
INSTITUTE

2. Neuroanatomical Sciences
LABORATORY

3. Functional Neuroanatomy
SECTION

4.
LOCATION

5. NINDB -36
SERIAL NO.

6. Relationship between Neurosecretion and milk ejection
PROJECT TITLE

7. Milton W. Brightman
PRINCIPAL INVESTIGATOR(S)

8. Junior personnel
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION.

Objectives: To determine whether or not a depletion of neurosecretory material occurs concomitantly with release of hormones from neurohypophysis in response to various stimuli.

Methods employed: Mice were allowed to nurse their young for various periods of time under different circumstances. The brains of these mice were stained by special methods. The amount of neurosecretory material was correlated with the period of suckling.

Major findings: The stimuli of suckling and of behavior associated with suckling resulted in a depletion of neurosecretory material from the hypothalamo-hypophysial system.

Significance: These experiments indicate a close relationship between the central nervous system and the endocrine system involving the pathway linking hypothalamus and neurohypophysis.

Proposed course of project: This work is being prepared for publication.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-36
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: Research

13. NO COOPERATING UNITS

14.

Honors, Awards, and Publications

16. PUBLICATION: None

17. NONE

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. N.I.N.D.B.
INSTITUTE

2. Laboratory of Biophysics
LABORATORY OR BRANCH

3.
SECTION

4.
LOCATION

5. NINDB-37
SERIAL NO.

6. Ion Permeabilities of Nerve Membranes.
A. Experimental investigations of the squid giant axon.
PROJECT TITLE

7. Moore, J. W.; Cole, K. S.
PRINCIPAL INVESTIGATORS

8. ---
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: The interpretation of nerve function in terms of fast ionic transports and the elucidation of the structures and mechanisms by which these transports are controlled.

Methods Employed: The instrumentation remains, fundamentally, the same as that first used at Woods Hole in 1947 to measure directly the ion current crossing the squid axon membrane between a long axial electrode within the electrode and an external concentric electrode after a controlled change of potential difference between these electrodes.

Major Findings: Although Hodgkin and Huxley subsequently improved the original design and used it very effectively, there remained serious sources of uncertainty or error. A micropipette electrode has been used for measurement of the intra axonal potential and control of the membrane current to minimize the effect of internal and external electrolytic resistances, to simplify the axial electrode design construction and operation, and to improve stability of both the equipment and the axon.

The new and modified equipment had to be transported to Woods Hole for extensive tests and development on the living axon. The analysis of the extensive data has only been started but, although axon survival and equipment stability were usually unsatisfactory, it seems probable that a small continuous inward membrane current flow of ions can considerably slow the usual deterioration process and also that the potassium potential can be considerably altered by a heavy outflux of these ions.

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Serial No.

Significance to NINDB Research: The recently developed concept and the measurements of the sodium and potassium ion movements across the squid axon membrane offer a new, highly specific and general approach to the factors underlying normal and pathological nervous processes which cannot as yet be investigated directly in higher animals and man.

Proposed Course of Project: The control circuits and axon cell components will be modified to improve speed, stability and survival before live squid can again be obtained.

R.P.C. - 2
December 1955

Budget Data Sheet

10. NINDB-37
SERIAL NO.

11.

BUDGET DATA:

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12. BUDGET ACTIVITY:

RESEARCH /X/

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13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

Marine Biological Laboratory.

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

NONE.

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. N.I.N.D.B.
INSTITUTE

2. Laboratory of Biophysics
LABORATORY OR BRANCH

3.
SECTION

4.
LOCATION

5. NINDB-38
SERIAL NO.

6. Ion Permeabilities of Nerve Membranes.
B. Theoretical investigations of the squid giant axon.
PROJECT TITLE

7. Cole, K. S.
PRINCIPAL INVESTIGATOR

8. Antosiewicz, H. A. (NBS); Moore, J. W.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: Evaluation of any limits within which the present differential equations may be used to determine the otherwise immeasurable fast ion movements across a normal nerve membrane; empirical modification of the equations for application to abnormal conditions; investigation of the structural and functional bases for the equations.

Methods Employed: Primary reliance will be placed on the National Bureau of Standards digital computer SEAC, which is coded to calculate the electrical potential and ion current responses to a variety of stimuli on the basis of the present equations. Linear and non-linear analogue computers will be employed as available and necessary for analysis and synthesis, using these and other empirical or theoretical equations.

Major Findings: The response of the nerve model to a stimulus is found to be all-or-none to a degree which is not only impossible to determine for a real nerve but also beyond the limit of resolution of SEAC -- which is about one part in twenty million. The SEAC code has been rewritten to permit more extensive and rapid analyses of the calculations and to investigate the characteristics of a uniformly propagating impulse. Extensive analysis has not yet produced a direct calculation for the speed of conduction while the original cut and try process is apparently progressing satisfactorily.

NINDB-38
SERIAL NO.

Significance to NINDB Research: The limited comparison between the broad generalizations of electrophysiology and calculations based upon empirical differential equations of normal membrane ion movements have been so satisfactory as to encourage the assumption that these movements and the mechanisms by which they are controlled are a fundamental component of normal and pathological nervous processes.

Proposed Course of Project: SEAC Calculations will be made to determine the velocity and wave form of a propagated impulse as a function of temperature and perhaps external sodium concentration. The threshold for simultaneous membrane excitation will be determined with maximum accuracy to guide a formal analysis of the equations and perhaps as a function of external sodium concentration. An analogue computer under design will be used to calculate the steady state alternating current ionic and membrane admittances and provide a basis for estimating the effect of external ions upon the equation parameters.

The possibility of obtaining faster solutions of the present and other equations under easily varied conditions will be an important factor in the design of a non-linear analogue computer.

R.P.C. - 2
December 1955

Budget Data Sheet

10. NINDB-38
SERIAL NO.

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11. BUDGET DATA:

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12. BUDGET ACTIVITY:

RESEARCH ☒

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13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

National Bureau of Standards.

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THIS PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

NONE.

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. N.I.N.D.B.
INSTITUTE

2. Laboratory of Biophysics
LABORATORY OR BRANCH

3.
SECTION

4.
LOCATION

5. NINDB-39
SERIAL NO.

6. Correlation of Acetylcholinesterase inhibition spectrum with nerve action.
PROJECT TITLE

7. Moore, J. W.
PRINCIPAL INVESTIGATOR

8. Friess, S. L. (NMRI)
OTHER INVESTIGATOR

9. PROJECT DESCRIPTION:

Objective: To attempt a characterization of the site of action of the drugs. The ultimate objective is to determine the mode of action.

Methods Exployed: The depression of the A fiber propagated action potential of a desheathed frog sciatic on passing through a drug chamber is observed. The ratio of the amplitudes of the impulse before and after passing the drug chamber is observed as a function of time. The velocity change caused by the drug is obtained from the change in the time interval between these impulses.

Major Findings: No correlation has been found between the in vitro enzymatic inhibition and the depression of the action potential for a series of compounds having inhibitory constants from one to four times that of eserine.

Significance to NINDB Research: These studies will aid in elucidating the structure of cholinesterase and its role in the function of nerves under normal and disturbed conditions.

Proposed Course: With the preliminary screening on the frog sciatic A fibers largely completed, attempts will probably be made to eliminate some of the ambiguities of interpretation inherent in the use of a multi-fiber preparation by testing the effects of some of the more interesting compounds on the intracellular potentials of a single lobster axon.

R.P.C. - 2
December 1955

Budget Data Sheet

10. NINDB-39
SERIAL NO.

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11. BUDGET DATA:

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12. BUDGET ACTIVITY:

RESEARCH ☒

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13. COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957:

Naval Medical Research Institute.

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH:

NONE.

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Neurochemistry
LABORATORY OR BRANCH

3. Lipid Chemistry
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NINDB-40
SERIAL NO.

6. Metabolism of Derivatives of Coenzyme A
PROJECT TITLE

7. Roscoe Brady
PRINCIPAL INVESTIGATOR(S)

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Project: Investigation of the occurrence and properties of cysteamine oxidase.

Objectives: As an outgrowth of studies on the enzymatic activity of derivatives of coenzyme A, a new enzyme has been discovered in extracts of tissues which oxidizes specifically the 2-mercaptoethylamine moiety of coenzyme A. We wish to study the tissue distribution and properties of this enzyme.

Methods employed: Standard enzyme fractionation procedures have already yielded a 15-fold purification of the enzyme, and further purification will be attempted with newer fractionation procedures. The fate of the cysteamine will be followed by the use of radioactive S^{35} cysteamine which has been prepared.

Major findings: The direct demonstration of an enzyme capable of oxidizing cysteamine is of especial interest to those interested in metabolic studies involving high-energy thiol esters. The immediate question is whether this enzyme will oxidize coenzyme A itself which is so important in biological oxidation. Only preliminary data have been obtained along these lines because the cost of substrate amounts of coenzyme A is prohibitive for studies with unpurified enzyme preparations.

Significance to Neurological Diseases Research: The undisputed paramount importance of the role of coenzyme A in biological energy-yielding reactions for the metabolism of nerve tissue as well as the synthesis of acetyl choline and fatty acids makes such a study as this of extreme fundamental interest. Any reaction involving coenzyme A could have far-reaching importance on the metabolism of nerve tissue, on conduction via acetyl choline, and on the biosynthesis of neural lipids which occur through the mediation of high energy coenzyme A complexes. Furthermore, taurine, a probable

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eventual product of this reaction is found in significant quantities in brain. The biosynthetic pathways of taurine formation and factors controlling these reactions merit investigation. The influence and the contribution of taurine itself and its intermediary compounds to cerebral function will be investigated.

Proposed course of project: An attempt will be made to ascertain if any other compounds can serve as substrate for this enzyme; also, we shall try to purify the enzyme in order to identify the products of the reaction, to investigate the stoichiometry of the reaction, and to study the kinetics and energetics of the reaction.

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December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-40
SERIAL NO.

11.
BUDGET DATA:

12. Research
BUDGET ACTIVITY

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1):

Mr. Richard Salvador, graduate student, Department of Pharmacology, The George Washington University School of Medicine.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES, OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH).

None

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-40
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

Brady, R.O.: The enzymatic activity of fluoroacetyl coenzyme A. Federation Proceedings, 14, 186 (1955)

Brady, R.O.: Fluoroacetyl coenzyme A. J. Biol. Chem., 217, 213 (1955)

Brady, R.O.: Enzymatic thioltransacetylation. Recent Progress in Neurochemistry and Allied Sciences. Paul D. Hoeber, Inc., New York, 1955.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

National Science Foundation travel award to the Third International Biochemical Congress, Brussels, Belgium, August 1955.

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December 1955

Analysis of NIH Program activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Neurochemistry
LABORATORY

2. Lipid Chemistry
SECTION

4. Bethesda, Maryland
LOCATION

5. NINDB-41
SERIAL NO.

6. Biosynthesis of Fatty Acids
PROJECT TITLE

7. Roscoe Brady
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Project: To investigate the mechanism of the stimulating effect of citric acid on the biosynthesis of fatty acids.

Objectives: It has been repeatedly observed that the addition of citric acid to an enzyme system capable of synthesizing fatty acids will stimulate the biosynthesis of fatty acids from 10 to 100-fold over the control value without citrate. We wish to learn the nature of this effect.

Methods employed: Sodium acetate labeled with radioactive carbon-14 is incubated with suitable water soluble enzyme systems capable of converting the acetate to long chain fatty acids. The fatty acids are recovered from the system after incubation and radioactivity determined.

Major findings: It has been found that the stimulating effect of citrate on fatty acid synthesis is due to its ability to cause the enzymatic reduction of diphospho, and particularly triphosphopyridine nucleotides. The requirement for citrate may be eliminated if reduced triphosphopyridine nucleotide is added to the enzyme system.

Significance to Neurological Diseases Research: Any discovery which contributes to our knowledge of the kinetics and mechanisms of fatty acid synthesis is of fundamental interest to neurology since the major non-aqueous component of nerve tissue is lipid in nature. Many of the degenerative diseases involving demyelination are directly related to lipid synthesis and breakdown, hence insight into this problem is of great concern to neurologists.

Proposed course of project: The project requires a study of other compounds such as isocitric acid and oxalsuccinic acid to determine their relative effectiveness for stimulating the system. Furthermore, a marked inhibition has been observed upon the addition of an excess of coenzyme A to this enzyme system although it has been shown that the system has an absolute dependence on coenzyme A. The mechanism of this inhibitor will be investigated.

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December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-41
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: RESEARCH

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.(S) (ITEM 1):

Mr. Abdel Megid Mamoon, Visiting Scientist, Egyptian National Research Council.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Neurochemistry
LABORATORY

3. Section on Lipid Chemistry
SECTION

4. Bethesda, Maryland
LOCATION

5. NINDB-42
SERIAL NO.

6. Biosynthesis of Cerebrosides
PROJECT TITLE

7. Roscoe Brady
PRINCIPAL INVESTIGATOR

8. Robert Burton
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Project: Investigation of the enzymatic synthesis of cerebrosides.

Objectives: We wish to discover the nature of the pathway for the biological synthesis of cerebrosides. Since a large proportion of brain lipid exists in the form of cerebrosides, and since certain conditions such as Gaucher's disease are associated with striking abnormalities in cerebroside metabolism, it is felt that knowledge of the metabolism of cerebrosides would be an important contribution.

Methods employed: Suitable methods for the isolation and characterization of cerebrosides have been developed. The biosynthesis of cerebroside has been investigated using carbon-14 labeled glucose, galactose, and a compound presumed to be an intermediate in this process, uridine-diphosphogalactose. Further methods have been developed for the preparation and microanalysis of sphingosine, one of the major constituents of the cerebroside molecule.

Major findings: It has been found that both radioactive glucose and galactose are incorporated *in vivo* into the cerebroside fraction of brain lipids. Since the involvement of uridine nucleotides in galactose metabolism is well established, an investigation of uridyl transferases in animal tissues was undertaken. Significant among the findings was the fact that brain tissue cannot incorporate galactose-1-phosphate into uridyl nucleotides although brain extracts appear to have an enzyme, galactokinase, capable of catalyzing the formation of galactose-1-phosphate.

Significance to Neurological Diseases Research: If galactose cannot be incorporated into uridyl nucleotides by brain, one of two possibilities arises; *a*, cerebroside synthesis does not necessarily occur via uridine diphosphogalactose, or *b*, if this intermediate is on the pathway of cerebroside synthesis, it renders the brain an unlikely site of the biosynthesis of cerebrosides and the process must be investigated in other tissues. The implications of these alternatives are of considerable fundamental importance in our search for knowledge of cerebroside metabolism and the untoward effects of its abnormalities in hereditary degenerative diseases of the central nervous system.

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Proposed course of project: An examination of the biosynthesis of cerebrosides *in vitro* will be undertaken in the forthcoming year. Preliminary data suggests that the reaction proceeds at a very slow rate and a search is in progress for the selection of optimal conditions to examine the process. Furthermore, it is essential that radiocarbon-14 cerebrosides be prepared in order to follow the metabolism of these compounds. Preliminary model syntheses have been successfully carried out although the total syntheses of a cerebroside has not as yet been accomplished. When these compounds are available, a study of their behavior will be undertaken.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-42
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY: RESEARCH

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANI-ZZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 1

Laboratory of Biochemistry and Nutrition, NIAMD

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None.

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-42
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

Maxwell, E.S., Kalckar, H.N., and Burton, R.M.: Galacto-waldenase and the enzymic incorporation of galactose-1-phosphate in mammalian tissues. Biochimica et Biophysica Acta, 18, 445, 1955.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

NONE.

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Neurochemistry
LABORATORY

3. Lipid Chemistry
SECTION

4. Bethesda, Maryland
LOCATION

5. NINDB-43
SERIAL NO.

6. Effect of LSD on Enzymatic Reactions
PROJECT TITLE

7. Roscoe Brady
PRINCIPAL INVESTIGATOR

8. Julius Axelrod
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Project: Investigation of the effect of the drug lysergic acid diethylamide (LSD) on enzymatic reactions.

Objectives: We wish to try to learn something of the mechanism of action of the drug upon the cerebral cortex.

Methods employed: These studies were undertaken with partially purified enzymes obtained from brain tissue for the most part. In particular, the effect of LSD on glutamine synthesis and transaminase as well as on the oxidation by brain tissue of radioactive C^{14}-labeled glucose and acetate have been investigated.

Major findings: To date, no clear cut influence of LSD on any particular enzymic reaction in brain has been demonstrated. We have, however, observed that extracts from certain micro-organisms can catalyze the formation of N-acetyl-LSD.

Significance to Neurological Diseases Research: The formation of N-acetyl-LSD is of potential interest since an energy-rich bond of unknown usefulness is formed at the expense of an equimolar amount of acetyl coenzyme A. The requirements of nerve tissue for acetyl coenzyme A for acetyl cholin and lipid synthesis are of great importance, and a reaction such as the formation of acetyl-LSD may represent a potential deviation from the normal metabolic processes. This would be particularly true if acetyl-LSD were hydrolyzed by brain with concomitant loss of the energy-rich bond as far as the maintenance of nerve function is concerned. The elucidation of such a reaction sequence could be of great potential significance in the study of mental disease, since the marked psychopathological effects of LSD are well documented.

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Proposed course of project: We wish to examine various extracts of brain tissue to learn if the enzymatic formation of N-acetyl LSD does indeed occur in such preparations. If the reaction can be demonstrated, an attempt to purify the enzyme and subsequent studies on the substrate specificity, kinetics, and free-energy change of the reaction will be undertaken.

Analysis of NIH Program Activities

Budget Data Sheet

10. **NINDB-43**
SERIAL NO.

11. BUDGET DATA

12. BUDGET ACTIVITY: RESEARCH

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH, INDICATE SERIAL NO.(S) (ITEM 1).

Section on Pharmacology, Clinical Investigation, NIMH.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH (BY SERIAL NO.(S) IF WITHIN NIH):

NONE.

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Neurochemistry
LABORATORY

3. Section on Lipid Chemistry
SECTION

4. Bethesda, Md.
LOCATION

5. NINDB-44
SERIAL NO.

6. Metabolism of Inositol
PROJECT TITLE

7. Roscoe Brady
PRINCIPAL INVESTIGATOR

8. Bernard Agranoff
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Project: Investigation of the metabolism of inositol, particularly with regard to its incorporation into brain diphosphoinositides.

Objectives: We wish to learn the nature of the biosynthetic pathway of the formation of the complex phospholipids of the brain which contain inositol.

Methods employed: The qualitative and quantitative determination of inositol has been until now dependent upon a tedious microbiological assay. We have recently developed, for the first time, column and paper chromatographic separation techniques for the identification and estimation of inositol. We are trying to develop methods for the organic synthesis of radiocarbon-14 labeled inositol. When these procedures have been perfected, we wish to study the enzymatic synthesis and degradation of inositol lipids.

Major findings: Dawson, in England, has reported, and his findings have been confirmed, that radioactive inorganic phosphate P^{32}, when injected into an animal, is very rapidly incorporated into brain inositol phospholipids.

Significance to Neurological Diseases Research: Dawson's observation is extremely interesting since this is the first indication of a rapid turnover of any portion of a complex cerebral lipid. Since the brain contains a proportionately large amount of lipid material, it is manifestly of interest to learn what function such compounds serve. An investigation into the metabolism of these compounds is potentially a very worthwhile study in view of the cerebral abnormalities associated with hereditary lipoidoses, etc.

Analysis of NIH Program Activities

Project Description Sheet

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Proposed course of project: We have already discovered that certain tissues contain enzymes capable of utilizing inositol as substrate. The nature of these enzymes, the cofactors required for their activity, and the products of the reaction will be identified. When radiocarbon-14 labeled inositol becomes available, we shall investigate further the metabolism of inositol and the inositol-containing lipids which cannot be followed by any other technique now available.

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December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-44
SERIAL NO.

11. BUDGET DATA

12. BUDGET ACTIVITY: Research

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH, INDICATE SERIAL NO.(S) (ITEM 1).

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH (BY SERIAL NO.(S) IF WITHIN NIH):

None

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December 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-44
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

This project is an outgrowth of a study on ribose metabolism which was completed during 1955. The report of this work has been accepted for publication in the J. Biol. Chem.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

None.

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Neurochemistry
LABORATORY

3. Lipid Chemistry
SECTION

4. Woods Hole, Mass.
LOCATION

5. NINDB-45
SERIAL NO.

6. The effect of intra-cellularly injected enzymes upon the impedance and action potential of the squid giant axon.
PROJECT TITLE

7. Roscoe Brady
PRINCIPAL INVESTIGATOR

8. W. H. Freygang, Jr. and C.S. Spyropoulos
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Project: Investigation of the effect of the intra-cellular injection of enzymes on nerve transmission.

Objectives: We wish to take the unusual opportunity of observing the effect of the intra-cellular injection of certain specific purified enzymes upon nerve transmission. The squid giant axon affords a particularly favorable system since action potentials and changes in impedance can be measured electrically whereas there is virtually no other cell or system of cells in which the effect of an injection of an enzyme can be performed, aside from obtaining immediately a measure of the response of a cell treated in such a fashion.

Methods employed: Transverse impedance and action potential measurements will be made on the squid axon. External electrodes will supply alternating current and will form one arm for Wheatstone bridge. Intracellular injection will be made into the portion of the axon resting between the electrodes. Certain enzymes which have been shown to be of importance for the metabolism of high energy phosphate and coenzyme A derivatives will be purified by standard procedures and injected intracellularly.

Major findings: The project has not as yet been undertaken.

Significance to Neurological Diseases Research: It is now quite firmly established that transmission of the nerve impulse is an enzymatic process. We wish to learn what effects will be brought about by altering the concentration of certain key enzymes which are believed to be involved in this process. The data obtained from such experiments could be of considerable importance in establishing the actual biochemical mechanisms involved in nerve transmission, a process which is as yet only vaguely understood.

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Project Description Sheet

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SERIAL NO.

Proposed course of project: See under Methods employed. Suitable micro-injection apparatus has been designed and constructed. Some of the enzymes to be tested have already been prepared. The problem will be executed in the summer of 1956 at the Marine Biological Laboratory, Woods Hole, Massachusetts.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-45
SERIAL NO.

11. BUDGET DATA

12. BUDGET ACTIVITY: Research

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957. IF COOPERATING UNIT IS WITHIN NIH, INDICATE SERIAL NO.(S) (ITEM 1):

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH (BY SERIAL NO.(S) IF WITHIN NIH).

None

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Neurochemistry
LABORATORY

3. Lipid Chemistry
SECTION

4. Bethesda, Md.
LOCATION

5. NINDB-46
SERIAL NO.

6. The relationship of nucleotides to lipid synthesis
PROJECT TITLE

7. Robert M. Burton
PRINCIPAL INVESTIGATOR

8. Roscoe Brady
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: The mechanisms involved in the synthesis of complex lipids of nervous tissue is poorly understood. Many of these reactions will be mediated by enzyme systems which will involve particularly nucleotides of hydrogen transfer, i.e., diphosphopyridine nucleotide and triphosphopyridine nucleotides, and nucleotides concerned with energy transfer, i.e., adenosine di- and tri-phosphates. By knowing the relationship of these nucleotides to lipid synthesis and their content in normal and pathological tissue, it may be possible to then correlate the nucleotide content and the activities of the associated enzyme systems with certain lipidoses and identify the metabolic lesions responsible.

Methods employed: The usual enzymatic techniques employed for studying enzyme systems will be used, i.e., spectrophotometry, manometry, fluorimetry, and radioisotope-labeled compounds.

Major findings: The project has not yet been started.

Significance to Neurological Diseases Research: Certain diseases of the nervous system are characterized by the over-production of complex-lipids, e.g., gangliosides in Tay-Sachs disease. Studies of this nature should lead to an understanding of the normal synthesis of these lipids and may lead, therefore, to a knowledge of the metabolic lesion responsible for either the over-production or the decreased rate of metabolism of these lipids in various nervous disorders.

Proposed course of project: Initially, studies will be carried out to determine the concentration, rate of synthesis, and rate of destruction, of these nucleotides in animals during the development of the nervous system and myelination. This will be correlated with oxidative reactions of brain tissue and with the rate of lipid synthesis. Finally, the individual enzyme systems involved will be isolated, characterized, and their properties described.

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December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-46
SERIAL NO.

11. BUDGET DATA

12. BUDGET ACTIVITY: Research

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH, INDICATE SERIAL NO.(S) (ITEM 1).

None

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH (BY SERIAL NO.(S) IF WITHIN NIH).

None

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Neurochemistry
LABORATORY

3. Lipid Chemistry
SECTION

4. Bethesda, Maryland
LOCATION

5. NINDB-47
SERIAL NO.

6. Toxicity of Neurophysiologically Active Chemicals
PROJECT TITLE

7. Robert M. Burton
PRINCIPAL INVESTIGATOR

8. Abraham Goldin
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Project: Protection of animals against the toxicity of neurophysiologically active agents.

Objectives: The mechanisms through which neurophysiological agents such as marsilid and reserpine exert their toxic properties are unknown. It is hoped by studying the relationships of these agents, at toxic doses, to other compounds which give protective action, that some of the underlying biochemical mechanisms may be elucidated. These relationships will serve, thereby, as a guide to the investigation of the individual enzyme systems that may be effected.

Methods employed: Classical pharmacological techniques will be used to investigate the action of these drugs individually and combined with reference to their immediate behavior and physiological effects and their toxicity. The *in vitro* studies will be carried out by the usual methods in enzymology, i.e., spectrophotometric and manometric studies.

Major findings: Dr. A. Goldin, NCI, has observed that marsilid potentiates the anesthesia produced by pentobarbital and that pentobarbital protects the animals against toxic doses of isonicotinic acid hydrazide. It has been found by Dr. N.O. Kaplan, The Johns Hopkins University, that both marsilid and isonicotinic acid hydrazide from analogs of diphosphopyridine nucleotides and that pentobarbital inhibits the enzyme responsible for the analog formation. Reserpine has been shown by Dr. B.B. Brodie, NHI, to potentiate hexabarbital hypnosis by causing the release of serotonin from its depots and that the serotonin itself is the potentiating agent. Lysergic acid diethylamide was shown to be an antagonist of both reserpine and serotonin potentiation of hypnosis. Continuing our studies on marsilid potentiation of anesthesia, it has been found that serotonin is less effective than marsilid as a potentiator of pentobarbital anesthesia, and that marsilid potentiation could not be blocked by lysergic acid diethyl amide. Studies with long-acting

NINDB-47
SERIAL NO.

anesthetics, as doriden and phenobarbital, suggest that the marsilid potentiation may be due to an inhibition of the metabolism of the anesthetic, The acute toxicity of reserpine is modified by marsilid, whereas serotonin increased the toxicity of reserpine. High single doses or multiple doses of serotonin failed to produce symptoms of reserpine toxicity. This is suggestive that reserpine toxicity may be due to other factors than the release of serotonin. Even though reserpine is a sedating agent, it exerts a potentiating effect upon d-amphetamine stimulation. The effective dose of d-amphetamine to produce convulsions and death is lowered when the animals receive reserpine. Neither serotonin nor serotonin-marsilid treatment potentiated the action of d-amphetamine. Both d-amphetamine and lysergic acid diethylamide appear to be effective agents for reversing the sedating action of reserpine. Preliminary experiments suggest that reserpine may be effective in increasing the survival time of mice with leucemia if the problem of reserpine acute toxicity can be overcome.

Significance to Neurological Diseases Research: The studies of drug potentiation and of the protection of the organism against the toxic action of certain compounds, may be fruitful in obtaining an understanding of basic physiological and biochemical processes. Specifically, by understanding the mechanism of marsilid potentiation of pentobarbital anesthesia, it may be possible to develop an approach to the elucidation of the very poorly understood phenomena of sleep and anesthesia. By learning how pentobarbital can protect animals against toxic manifestations of isonicotinic acid hydrazide, a convulsant, it may be possible to investigate the neurophysiolcgical processes involved in sedatives and stimulation.

Proposed course of project: Studies will be continued to correlate structure and physiological response of those drugs that are potentiated by reserpine and related compounds, and, in particular, those compounds that will protect the host against the toxic manifestations of the neurophysiologically active agent. In vitro studies will be undertaken to investigate possible biochemical sites of action of these compounds.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-47
SERIAL NO.

11. BUDGET DATA

12. BUDGET ACTIVITY: Research

13. IDENTIDY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH, INDICATE SERIAL NO.(S) (ITEM 1).

This project is being carried out cooperatively with the Section on Biochemical Pharmacology, Laboratory of Chemical Pharmacology, National Cancer Institute.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANCE OF PERSONNEL, FACILITIES, OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

This project complements research being carried out by the Laboratory of Chemical Pharmacology, National Heart Institute.

R.P.C. - 1
December 1955 Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Laboratory of Neurophysiology
LABORATORY OR BRANCH

3. Special Senses
SECTION

4. Marine Biological Laboratory
Woods Hole, Massachusetts
LOCATION (IF OTHER THAN BETHESDA)

5. **NINDB-48**
SERIAL NO.

6. Studies on the process of action potential production
PROJECT TITLE

7. I. Tasaki
PRINCIPAL INVESTIGATOR

8. L. N. Tasaki, K. Frank and S. Hagiwara
OTHER INVESTIGATORS

9. Objectives: The objective of this study is to clarify the mechanism of action potential production in various excitable tissues.

Methods Employed: The technique of recording single node action potentials has been used for studies on the amphibian myelinated nerve fiber. Hyperfine microelectrodes were used for studies on the muscle fiber. The techniques of intracellular canulation will be used for studies on the squid giant axons.

Major Findings: 1. Measurements have shown that the capacity of the nodal membrane of the frog nerve fiber is approximately 1.5×10^{-12} farad. It was concluded that this capacity is too small to play a significant role in the process of action production at the node of Ranvier. Evidence was obtained showing that the major portion of the action current of a single node has nothing to do with charging or discharging of the membrane capacity. 2. It was possible to vary the membrane current during activity of a single node (in the range between zero and 10^{-9} amp.) without modifying the major portion of the nodal action potential. 3. A short pulse of strong inward current through an active nodal membrane abruptly stopped, or abolished, the activity of the node. This abolition of an action potential was roughly all-or-none and occurred when the membrane potential was lowered approximately to the critical level required for initiating an action potential in a resting node. Initiation and abolition of action potentials can be explained in terms of transition between two stable levels of membrane potential. 4. During passage of an outward current through the nodal membrane, a progressive change occurred in the membrane which could best be described as an increase in the membrane-e.m.f. associated with a slight reduction in the membrane resistance. This progressive change, which resulted in the accommodative change in threshold, occurred in a node immersed in a sodium-free Ringer as well as in normal Ringer. 5. It was found

Project Description Sheet

that the resistance of the muscle fiber membrane remains almost unchanged when a strong outward current reduces the membrane potential by 60 to 120 mV. This finding was interpreted as indicating that the falling phase of the muscle action potential is not caused by outflux of potassium ions across the membrane. In connection with this study, an accurate method of measuring the membrane capacity by A.C. was developed. 6. The results presented above strongly suggest that the action potential production in the myelinated nerve fiber and in the striated muscle fiber cannot be explained in terms of the ionic theory.

Significance to Neurology Research: Fundamental to neurophysiological research.

Proposed Course of Project: Further studies on the myelinated nerve fiber and the striated muscle fiber are required to clarify the mechanism of action potential production in these tissues. In the period between June and July 1956, research work at Marine Biological Laboratory at Woods Hole, Massachusetts is planned; the purpose is to examine effects of various ezyme poisons introduced into the axoplasm on the resting and action potentials of the squid giant axon.

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-48
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY:

Research

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM NO):

Study No. 2 was carried out in collaboration with K. Frank of the Section on Spinal Cord in the Laboratory of Neurophysiology, NINDB.

Studies on the muscle fiber were carried out in collaboration with Dr. S. Hagiwara of the Department of Biology, University of California in Los Angeles.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH):

None.

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. **NINDB-48**
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

1. New measurements of the capacity and the resistance of the myelin sheath and the nodal membrane of the isolated frog nerve fiber. Amer. J. Physiol., 181: 639, 1955.
2. Measurement of the action potential of myelinated nerve fiber (with K. Frank). Amer. J. Physiol., 182: 572, 1955.
3. Studies on the process of production of an action potential at a single node of Ranvier. Microphysiologie Comparee des Elements Excitable 67 ēme Collogue International, Centre National de la Rechezche Scientifique, Paris (in Press).

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

None.

R.P.C. - 1
December 1955 Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Laboratory of Neurophysiology
LABORATORY OR BRANCH

3. Special Senses
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NINDB-49
SERIAL NO.

6. The parallelism between the action potential, action current, and membrane resistance at a node of Ranvier.
PROJECT TITLE

7. I. Tasaki and W. H. Freygang, Jr.
PRINCIPAL INVESTIGATORS

8.
OTHER INVESTIGATORS

9. Objectives: The primary objective of this study is to describe accurately the relative temporal courses of the voltage across the cell membrane at a node of Ranvier, the flow of current through the node, and the changes in nodal membrane resistance. These quantities are measured during the activity cycle of a single node of Ranvier of an isolated frog or toad motor axon.

Methods Employed: The changes in membrane potential are measured by the method of Tasaki and Frank (Amer. J. Physiol., 1955, 182, 572). Action current is monitored in an external circuit which connects the active node to an adjacent inactive node. Membrane resistance at the active node is measured by two methods: 1. As proportional to the change in voltage across the node produced by a constant current pulse, 2. by including the active node in one arm of a Wheatstone bridge.

Major Findings: Except for minor variations occurring early in the activity cycle, the temporal courses of voltage, current, and resistance are parallel.

Significance to Neurology Research: An analysis of these results shows that, if the widely accepted model of the membrane proposed by Hodgkin and Huxley applies to the nodal membrane, the membrane can become permeable to only one ion species during activity.

Proposed Course of Project: No further work is planned.

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December 1955 Analysis of NIH Program Activities

Budget Data Sheet

10. **NINDB-49**
SERIAL NO.

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11. BUDGET DATA:

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12. BUDGET ACTIVITY:

Research

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13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM NO):

None.

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH):

None.

R.P.C. - 1
December 1955 Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Laboratory of Neurophysiology
LABORATORY OR BRANCH

3. Special Senses
SECTION

4. Marine Biological Laboratory
Woods Hole, Massachusetts
LOCATION (IF OTHER THAN BETHESDA)

5. NINDB-50
SERIAL NO.

6. Analysis of the action potential of the nerve cell body
PROJECT TITLE

7. I. Tasaki and S. Hagiwara
PRINCIPAL INVESTIGATORS

8. L. N. Tasaki
OTHER INVESTIGATORS

9. Objectives: In August, 1955, Dr. Hagiwara found that the giant nerve cells behind the vertebral column of certain blowfish (Plectognathi) are excellent material for electrophysiological studies ith submicroscopic microelectrode. These are at present the only nerve cells into which a micoelectrode has been introduced under direct visual control. Studies on these giant nerve cells will promote our understanding of the function of the nerve cell. Dr. Hagiwara is expected to join our section for a period of one year beginning in July, 1956.

Methods Employed:

Major Findings On two blowfish obtained toward the end of the last summer, Dr. Hagiwara has successfully introduced microelectrodes into the giant nerve cell and recorded a large resting potential (approx. 70 mV) and somewhat slow action potential in response to stimulation of the peripheral nerve.

Significance to Neurology Research: To futher our understanding of the function of the nerve cells.

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December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. **NINDB-50**
SERIAL NO.

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11. BUDGET DATA:

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12. BUDGET ACTIVITY:

Research

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13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM NO):

None.

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14. IF THIS PROJECT DUPLICATES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH):

None.

R.P.C. - 3
December 1955 Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-50
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

J. Gen. Physiol. Nov. 1955, 39: No. 2.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

R.P.C. - 1
December 1955 Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Laboratory of Neurophysiology
LABORATORY OR BRANCH

3. Special Senses
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NINDB-51
SERIAL NO.

6. Analysis of the sensory mechanism in the inner ear
PROJECT TITLE

7. I. Tasaki and L. N. Tasaki
PRINCIPAL INVESTIGATORS

8.
OTHER INVESTIGATORS

9. Objectives: The objective of this project is to clarify the mechanism by which nerve impulses are initiated in the auditory nerve fibers in response to acoustic stimulation.

Method Employed: The cochlea of an anesthetized guinea pig is exposed and small holes are drilled through its bony wall. Micropipettes for recording the cochlear potentials and for injection of various chemicals are introduced into the endo- and perilymphatic spaces. The changes in the cochlear potentials (nerve, microphonic and d.c. potentials) are analyzed to clarify the auditory mechanism.

Major Findings: Anoxia and injection of azide or cyanide into the endolymphatic space were found to reversibly reduce the cochlear d.c. potential and the nerve and microphonic responses. This finding suggests that some oxidative reaction is playing a decisive role in the maintenance of the excitability of the inner ear.

Significance to Neurology Research: It has been shown previously (Tasaki, Davis and Eldridge, J. Acous. Soc. Amer. September 1954) that the variation in the large potential drop across the hair-bearing end of the hair-cells is the first physiological process caused by acoustic stimuli applied to the cochlea. Further analysis of this large hair-cell potential is expected to lead us to a better understanding of the process of normal hearing and of the cause of certain types of deafness.

Proposed Course of Project: The effect of carbon monoxide on the cochlear potentials will be examined. Attempts will be made to see if the cytochrome system plays any role in the auditory mechanism.

R.P.C. - 2
December 1955 Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-51
SERIAL NO.

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11. BUDGET DATA:

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12. BUDGET ACTIVITY:

Research

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13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957: IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM NO):

None.

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH):

None.

R.P.C. - 1
December 1955 Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Laboratory of Neurophysiology
LABORATORY OR BRANCH

3. Special Senses
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. NINDB-52
SERIAL NO.

6. Analysis of the changes in the duration of electric responses of single nerve fibers following repetitive stimulation.
PROJECT TITLE

7. Constantine S. Spyropoulos
PRINCIPAL INVESTIGATOR

8. I. Tasaki
OTHER INVESTIGATORS

9. Objectives: To study the effects of repetitive stimulation on single fiber activity.

Methods Employed: The bridge insulator method of recording single nerve fiber responses was employed.

Major Findings: Repetitive stimulation modified the properties of the nerve fiber in a very remarkable manner. The most conspicuous modification was a multifold increase in the duration of the response associated with a characteristic change in the time course of the response. These modifications remained for many hours (possibly for days) after stimulation. A similar modification was observed in the nerve fibers stimulated in vivo. The effects of chemicals, temperature changes and hydrostatic pressure upon the response of a repetitively stimulated nerve fiber were different from the effects of these agents upon a normal (resting) nerve fiber. These changes were reversible.

Significance to Neurology Research: It is possible that the changes in the properties of the nerve fiber caused by repetitive stimulation are related to memory or learning. There is some similarity between the action potential of the heart muscle and the response of a repetitively stimulated nerve fiber; in both cases the response is very sensitive to temperature changes and also to various chemicals. This similarity seems to explain some aspects of the peculiarity of the heart muscle action potentials.

Proposed Course of Project:

10. **NINDB-52**
SERIAL NO.

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11. BUDGET DATA:

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12. BUDGET ACTIVITY:

Research

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13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957, IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 10):

None.

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14. IF THIS PROJECT PARALLELS, COMPLEMENTS, OR IS PARALLELED BY ONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH PROJECTS: (BY SERIAL NO(S) IF WITHIN NIH):

[illegible].C. - 3
December 1955

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-52
SERIAL NO.

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16. LIST PUBLICATIONS OF [illegible] THIS PROJECT DURING CALENDAR YEAR 1955:

Studies on the process of production of an action potential at a single node of Ranvier. Microphysiologie Comparee des Elements Excitable 67 [illegible]e Collegue International, Centre National de la Recherche Scientifigue, Paris. (In press) Presented by Dr. I. Tasaki in June, 1955.

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17. LIST HONORS AND AWARDS TO PERSONNEL [illegible] TO THE PROJECT DURING CALENDAR YEAR 1955:

None.

I.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Laboratory of Neurophysiology
LABORATORY OR BRANCH

3. Special Senses
SECTION

4. ____________
LOCATION (IF OTHER THAN BETHESDA)

5. **NINDB-53**
SERIAL NO.

6. The effects of hydrostatic pressure and temperature on single nerve fiber activity.
PROJECT TITLE

7. Constantine S. Spyropoulos
PRINCIPAL INVESTIGATOR(S)

8. ____________
OTHER INVESTIGATORS

9. Objectives: There is some question as to whether the primary processes underlying nerve excitation are physical (ionic) or chemical (enzymatic). The combined effects of temperature and pressure changes on enzymatic reactions are fairly characteristic and often predictable. It seems possible, therefore, to decide whether the nerve activity is enzymatic or not by examining the effects of pressure and temperature changes on single nerve fibers.

Methods Employed: The "bridge-insulator method" of recording single nerve fiber responses was employed. An AMINCO super-pressure chamber and pump assembly was used for generating high hydrostatic pressure.

Major Findings: The responses of single nerve fibers were found to be very sensitive to changes in hydrostatic pressure. The amplitude, duration and latency of responses and the threshold for electric stimulation were measured under various hydrostatic pressures.

Significance to Neurology Research: This research is expected to clarify some aspects of the metabolism of neurons.

Proposed course of project: Continue indefinitely.

R.P.C. - 2
December 1955

Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-53
SERIAL NO.

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11. BUDGET DATA:

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12. BUDGET ACTIVITY:

Research

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13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATION, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957; IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM 10).

None.

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14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH):

None.

R.P.C. - 1
December 1955 Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Laboratory of Neurophysiology
LABORATORY OR BRANCH

3. Spinal Cord
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. **NINDB-54**
SERIAL NO.

6. Origin of rhythmic activity in the spinal cord
PROJECT TITLE

7. K. Frank, R. Morrell, and M.G.F. Fuortes
PRINCIPAL INVESTIGATORS

8. M. Becker
OTHER INVESTIGATORS

9. Objectives: This project has as its major goal the determination of the origin of the rhythm of trains of impulses recorded from single nerve cells in the spinal cord. Specifically, it is desired to know whether the pacemaker for a train of nerve impulses coming from a single cell lies in that cell or outside it.

Methods Employed: Intracellular recording and stimulation of single nerve cell activity. 1. Resetting of spontaneous and elicited rhythmic activity by excitation via different routes. 2. Modification of rhythmic activity by manipulation of internal and immediate external environment of nerve cells. Transmembrane polarizing currents, changes in ionic composition of cytoplasm and drugs delivered outside the penetrated cell permit such modification of rhythms. 3. Modification of rhythmic action by degeneration of terminal endings.

Major Findings: Direct excitation of motor horn cells through the microelectrode also resets their rhythmic activity as does antidromic and orthodromic excitation. This confirms the previous conclusion that motor horn cells generate their own rhythms in response to asynchronous synaptic bombardment. 2. Each impulse in a train of impulses is elicited when the cell membrane is depolarized to a critical potential regardless of how depolarization is achieved. The impulse abolishes at least part of the effect of previous synaptic depolarization and temporarily raises the threshold for re-excitation. The rate at which synaptic activity can depolarize the membrane to this threshold level determines the frequency of the train but not the phase.

Significance to Neurology Research: This is one phase of a broad attack on the detailed behavior of rhythmical elements in the normal and pathological nervous system.

Project Description Sheet

Proposed Course of Project: To date the extension of the above resetting methods to interneurons has not been successful partly due to their small size but mostly due to the irregular nature of their rhythms. A new attack is therefore desired emphasizing possible alterations in the mean impulse frequency of these cells by local changes.

Further knowledge is required regarding the roles played by various ions in the rhythmic activity of motor horn cells. This and their ability to function after degeneration of neighboring neurons will be the subject of future research on the project.

R.P.C. - 2
December 1955 Analysis of NIH Program Activities

Budget Data Sheet

10. NINDB-54
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY:

Research

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957, IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM NO):

This has been a cooperative project with Dr. M.G.F. Fuortes of the research staff of the Army Medical Center at Walter Reed Hospital without exchange of funds.

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH):

While this project is actually a part of the main project, "Mechanisms of interaction between neurons in the spinal cord," it has in the past been treated separately. It is not planned to continue this as a separate project beyond July 1956.

R.P.C. - 1
December 1955

Analysis of NIH Program Activities

Project Description Sheet

1. Neurological Diseases and Blindness
INSTITUTE

2. Laboratory of Neurophysiology
LABORATORY OR BRANCH

3. Spinal Cord
SECTION

4.
LOCATION (IF OTHER THAN BETHESDA)

5. **NINDB-55**
SERIAL NO.

6. Mechanisms of interaction between neurons in the spinal cord
PROJECT TITLE

7. K. Frank, M.G.F. Fuortes, and R. Morrell
PRINCIPAL INVESTIGATORS

8. M. Becker
OTHER INVESTIGATORS

9. Objectives: The broad objectives of this, the main project of the Spinal Cord Section, are the investigation of basic mechanisms of neuronal interaction of the central nervous system operating in the spinal cord.

Methods Employed: The principal tool used in these investigations is the salt-filled ultramicroelectrode. Electrodes of this type are placed inside single nerve cells or fibers in the spinal cord and are used to record the electrical signs of nervous activity, either spontaneous or in response to various stimuli applied to the nervous system or to the penetrated cell directly through the recording electrode.

To the above general methods will be added the use of multiple microelectrodes permitting manipulation of internal and external chemical environment of the penetrated nerve cell.

A method planned in cooperation with Dr. G. Rasmussen of the Laboratory of Neuroanatomical Sciences involves a study of the behavior of spinal neurons in animals prepared with various chronic lesions. The manner in which such lesions modify single cell behavior could add to both anatomical and physiological knowledge of the spinal cord.

Major Findings: 1. It has been determined that the excitation of the motoneuron by three routes (orthodromic, antidromic and direct depolarization) all involve a similar discontinuous transition of states which may mean, as suggested by Gerard, that the motoneuron soma is normally bypassed for synaptic excitation. 2. Several of the equivalent electrical constants of the motoneuron membrane have been measured: resting membrane resistance about 1 megohm, active membrane resistance about 0.2 megohm, time constant about 1 msec.

R.P.C. - 1 (continued)
December 1955

NINDB-55
SERIAL NO.

Project Description Sheet

Significance to Neurology Research: These findings provide basic information regarding the types of interactions occurring between neurons and therefore add to the understanding of the behavior of the central nervous system. The application of such information to the treatment of diseases of the nervous system is a real hope for the distant future.

Proposed Course of Project: Emphasis in future experiments will be on further elucidation of the manner in which neuron interaction is modified by controllable environmental factors. A study of the roles of intracellular ions on synaptic transmission and inhibition will be of particular interest. It is planned to explore the use of multiple microelectrodes each containing a different electrolyte.

Another problem planned for investigation is the direct identification of the neuron or structure from which electrical potentials are recorded.

R.P.C. - 2
December 1955 Analysis of NIH Program Activities

Budget Data Sheet

10. **NINDB-55**
SERIAL NO.

11. BUDGET DATA:

12. BUDGET ACTIVITY:

Research

13. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN EITHER 1956 or 1957, IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S) (ITEM NO):

This is a cooperative project carried out in part with Dr. M.G.F. Fuortes of the research staff of the Army Medical School at Walter Reed Hospital and Dr. G. Rasmussen, NINDB, "The precise terminations of certain tracts and other connections of the brain stem and spinal cord."

14. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S) IF WITHIN NIH):

None

Analysis of NIH Program Activities

Honors, Awards, and Publications Sheet

15. NINDB-55
SERIAL NO.

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1955:

A. K. Frank and M.G.F. Fuortes. Potentials recorded from the spinal cord with microelectrodes. J. Physiology (in press).

B. K. Frank and M.G.F. Fuortes. Unitary activity of spinal interneurons of cats. J. Physiol. (in press).

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1955:

Conference on "The microneurophysiology of the synapse" at Seattle, Washington, 1955.

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